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Epidemic of Lung Cancer or Artifact of Classification in the State of Kentucky?

Beatrice Simo
East Tennessee State University

Epidemic of Lung Cancer or Artifact of Classification in the State of Kentucky?

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by
Beatrice Simo
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Dr. Tim Earl Aldrich, Chair
Dr. Joanne Walker Flowers
Dr. Wanzer John Drane

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ABSTRACT

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Lung cancer remains the leading cause of cancer deaths in the United States despite public health campaigns aimed at reducing its rate of mortality. Kentucky is the state with the highest lung cancer incidence and mortality. This study aims to assess the impact of misclassification of cause of death from Lung Cancer in Kentucky for the period 1979 to 2002. We will examine the potential competing classification of death for two other smoking-related diseases, Chronic Obstructive Pulmonary Disease (COPD) and Emphysema. Age-adjusted mortality rates for these diseases for white males were obtained from the National Center for Health Statistics. There was little evidence that any misclassification between COPD or Emphysema mortality rates was in agreement with the rising lung cancer rates in Kentucky. The long-term increase in lung cancer mortality in Kentucky is likely because of a combination of risk effects between smoking and other risk-factors for this disease.

DEDICATION

Foremost, I give the glory to almighty God for inspiring me to choose this Master of Public Health program of study and carrying me through its completion. I would like to honor my beloved deceased father, Mr. Michel Kenmegne, and my lovely mother, Mrs. Marie-Louise Modjo, for their love and self-sacrifice without which I would never have gone this far with school. Thank you for believing in me; I love you and miss you all the time. I am also indebted to my brothers and sisters for their love and support.

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CHAPTER 1

INTRODUCTION

In 2005 lung cancer caused more deaths worldwide than any other type of cancer; there were 1.3 million lung cancer deaths from a total of 7.6 million cancer deaths (World Health Organization, 2006). In the United States lung cancer also remained the deadliest of all cancers. It is projected that about 174,470 new cases and nearly 162,500 deaths will occur in the US in 2006. Research has proven that among the risk factors for the cancer of the lungs nearly 90% is attributable to active cigarette smoking. Cigarette smoking also appears to be the most preventable cause for lung cancer (American Cancer Society, 2006).

Statement of the Problem

The risk for lung cancer varies from one state to another in the United States. Kentucky is not only the one with the highest lung cancer incidence and mortality, but its rates, which have increased over time, are surprisingly far greater than the national average (American Cancer Society, 2006). For instance, the lung cancer incidence rate for the U.S. was 62.3 per 100,000 compared to 97.49 per 100,000 for Kentucky in 2000 (Hopenhayen et al., 2003). In 2002, there were 3,100 lung cancer deaths in Kentucky. Two years later the number of death rates rose to 3,380 (Kavanagh, 2002). The number of deaths from lung cancer in that state will continue to increase with an estimated 3,500 in 2006 (American Cancer Society, 2006). Elevated smoking level among Kentuckians has been the main explanation for this trend, which has been ongoing for years. Usually Kentucky is either the first or second state with the highest smoking rates, and smoking rates among its youth are usually highest. In 2003 the prevalence of cigarette smoking in Kentucky was 30.8% (MMWR, 2003). The following year, although Kentucky was still number one in the U.S., its smoking rates decreased to 27.7% (MMWR, 2004).

Figure 1 below shows how the increase and decrease in smoking consumption are correlated with lung cancer rates (American Cancer Society, 2006).

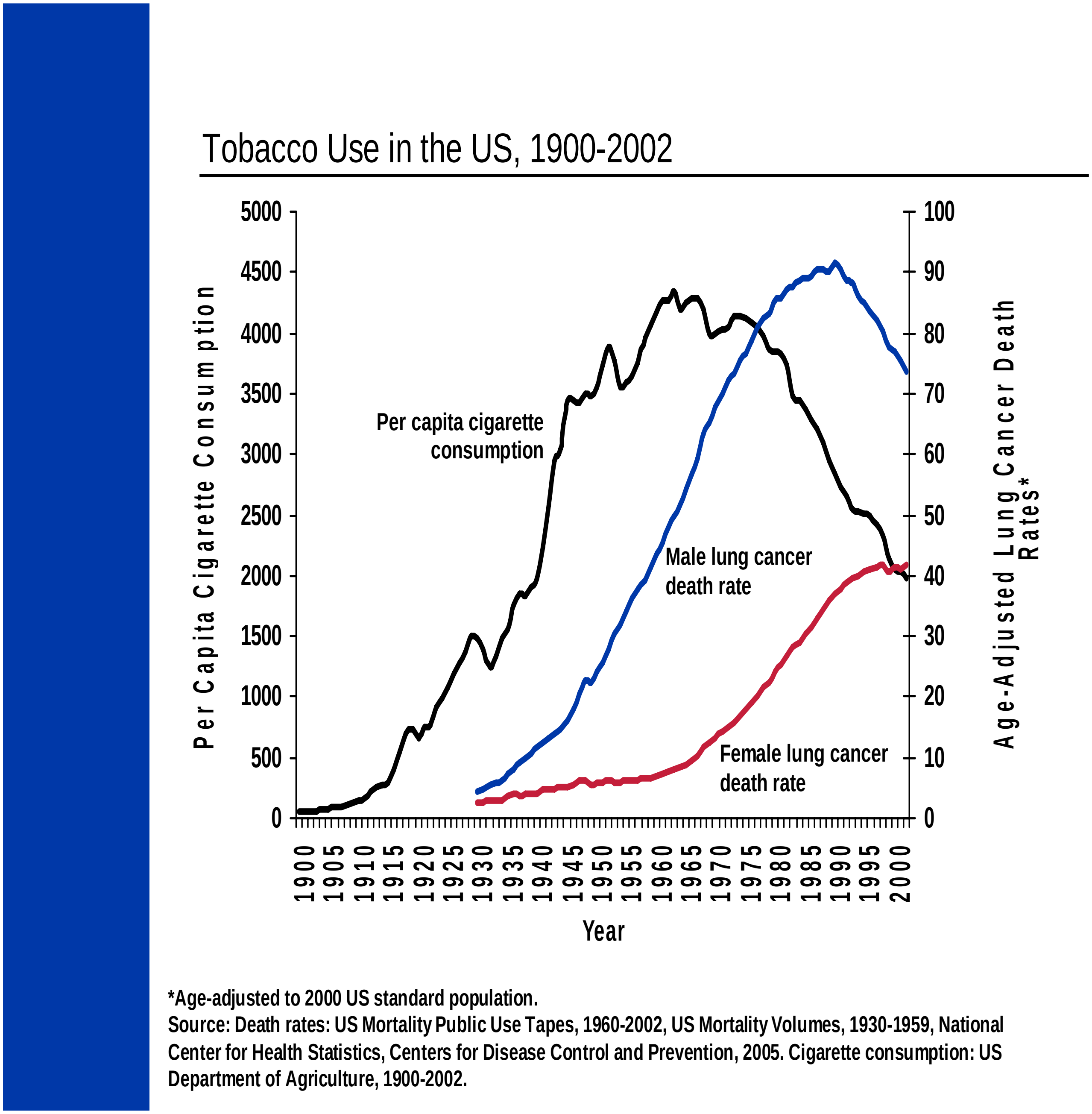

Figure 1. Tobacco Use and Lung Cancer Mortality in the U.S., 1900-2002.

Multiple public health programs designed to alleviate the burden of lung cancer have been established. For instance, although Healthy People 2000 goals to decrease smoking prevalence in the US did not succeed completely, a good number of people made the smart decision to embrace healthier habits. Their choice not to engage in smoking positively impacted lung cancer rates. In1991 this resulted in a decline for Lung cancer deaths for the first time in 50 years. Another decrease occurred the following year, and then followed consistently to 2000. "Healthy People" continues to follow its aim at reducing lung cancer death rates. Its target for year 2010 was set at 44.9 deaths per 100,000 population from a baseline of 57.6 lung cancer deaths per 100,000 population in 1998 (Health People 2010). Beyond this trend, there may be additional factors that influence the diagnosis of lung cancer in Kentuckians.

The specific objective of this study is to scrutinize the impact of misclassification of Cause of Death from lung cancer in Kentucky for the period 1979 to 2002. The national cancer mortality maps for this time period indicate an alarming increase in lung cancer mortality for the state. (Appendix A) This has made Kentucky the focal state for lung cancer in the nation. Although elevated smoking rates in Kentuckians correlate with this rise, as far as cause-specific mortality rates are concerned, they might not explain the temporal trend. One may suspect that increasing access to health care for Rural and Appalachian persons has led to improvement in lung cancer mortality misclassification over the interval. Improvement in the classification of lung cancer deaths in Kentucky may provide an explanation for the consistently elevated lung cancer death rates for the state over time.

Figure 2 shows the underlying-cause mortality data for white males for the entire U.S. compared to Kentucky (National Center for Heath Statistics). This graph depicts how the

Kentucky rate has surpassed that of the U.S. in the last 30 years. Also shown are the relative patterns for the two causes of death (COPD and Emphysema) that this thesis will examine.

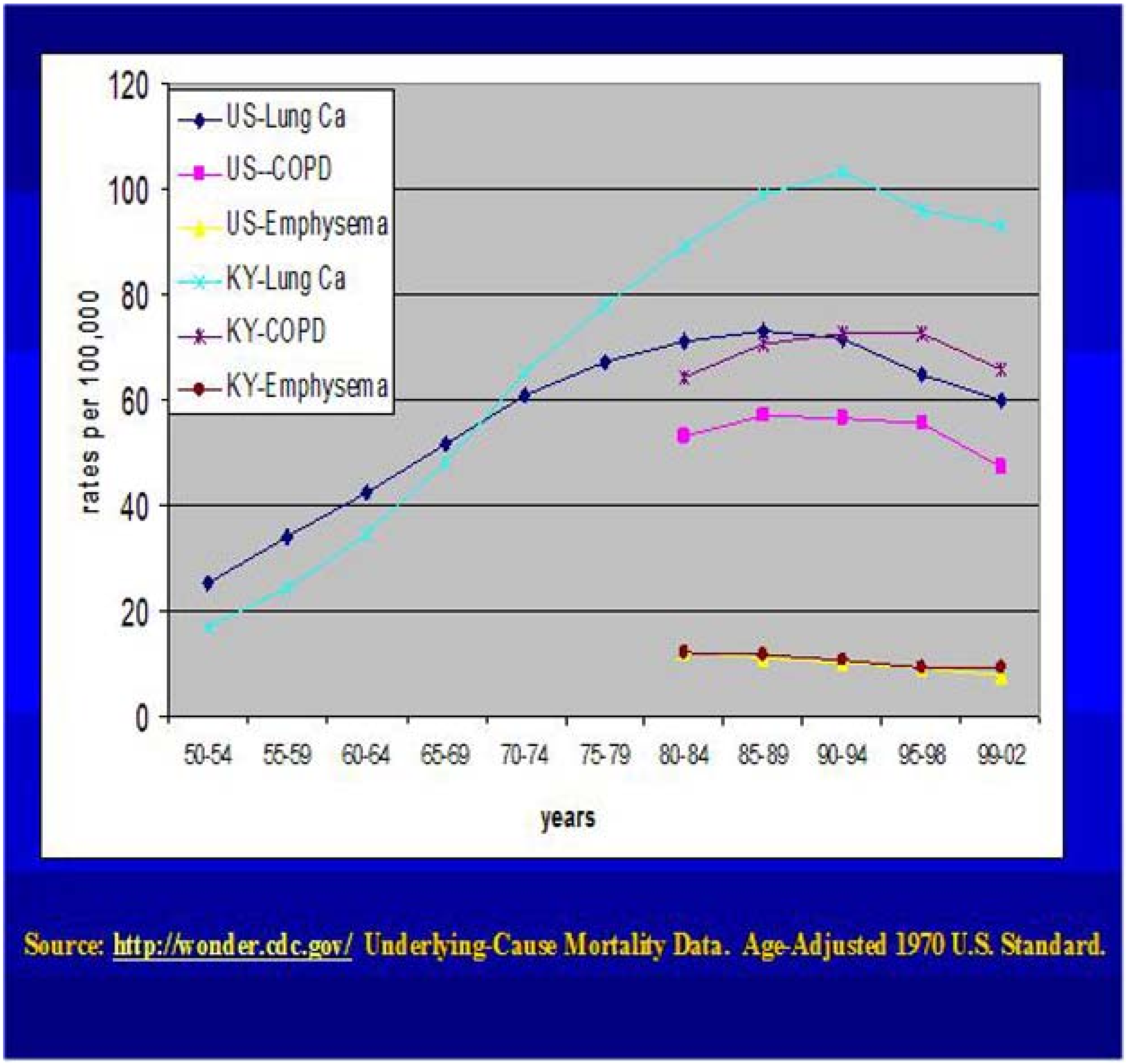

Figure 2. United States Lung Cancer, COPD, and Emphysema Mortality Rates Versus Kentucky Lung Cancer, COPD, and Emphysema Mortality Rates.

Overview of Study

This study used white male lung cancer, COPD, and Emphysema data from the National Center for Health Statistics for calendar years 1979 through 2003. Proportion of variations between lung cancer because of COPD and emphysema were determined (CDC Wonder, 2005).

Significance of Study

Very few studies on the geographic variation in lung cancer have been done to date. This appears to relate to the acceptance of the dominant risk due to cigarette smoking. Research into "other" factors influencing lung cancer risk were deemed lower priority. Lung cancer rates have continued to increase for more than a decade despite public health efforts fostering smoking cessation. So, this study will examine one potential explanation, the impact of competing classification of death for two other smoking-related diseases: COPD and Emphysema.

Research Questions

Could the reason why we have not seen consistent results for a decrease in lung cancer mortality rates yet be because of the time lag between smoking cessation and the biologic manifestations from smoking? In addition, as smoking leads to other diseases besides lung cancer, could a diagnostic precision bias pose an artifact in the apparent lung cancer pattern in Kentucky? Or could the misclassification of causes of death represent an effect of inaccuracy (Wells et al., 1990)? If there is no evidence of misclassification, what factors in addition to smoking patterns in Kentucky might need further consideration?

CHAPTER 2

REVIEW OF THE RELATED LITTERATURE

The 20th century brought much improvement in human life. Medical innovations played a huge role in the reduction, in some case the eradication (e.g. smallpox), of certain diseases such as tuberculosis, pneumonia, and typhoid fever among others. Other health conditions, however, for which the rates of occurrence were not very significant prior to the beginning of the century, increased at an unpredictable rate. One of such morbidities is cancer (MMWR, 1999).

Among cancerous diseases in the United States lung cancer was not very pronounced at the beginning of the century. This condition started peaking by the 1930s at an alarming rate to reach an epidemic level, which has persisted long enough to cross to the next century. Epidemiologic studies conducted to unravel lung cancer causality led researchers to establish smoking as its main risk factor in the 1950s (Samet, 1993).

Up to the first half of the 20th century cigarette smoking was very popular and considered an accepted behavior in industrialized countries; the population of smokers reached up to 80% in countries such as the United Kingdom. Among the factors that led to widespread cigarette consumption early in the 20th century were introduction of addictive properties to cigarette, improvements in its mass production and transportation, its promotion via advertising, and its embracement by women because of social changes promoting women liberalism (Encyclopedia Britanica Online, 2006). All these trends caused annual per capita consumption of cigarette in the United States to increase from 54 cigarettes at the beginning of the century to 4,345 cigarettes in 1963 (MMWR, 2003).

Increased cigarette consumption caused lung cancer to become the leading cause of cancer mortality among men after the early 1950s. In 1987, it also became the leading cause of cancer deaths in women, outranking breast cancer. The alarming death toll caused by lung cancer led to public health campaigns aimed at reducing tobacco consumption. Consumption of cigarette then declined to 2,261 per capita in 1998. By the end of the century, variation in smoking patterns led to significant decline in lung cancer incidence among men (Alberg & Samet, 2003). Despite this decline in cigarette smoking, lung cancer mortality still remains a health burden in the U.S. This is certainly what led to the search for another potential justification for the rising lung cancer rates. Several researchers came up with another explanation for the rising lung cancer rates. They posited that classification of lung cancer on death certificate may vary over time.

Previous Research on Lung Cancer Misclassification

Modern society seems to have brought about a shift upwards in the incidence of pulmonary morbidities. This likely increasing trend reflects improvements with diagnostic capabilities. Wells et al. (1990) analyzed medical records for patients primarily diagnosed with lung cancer discharged from Yale-New Haven Hospital during 1921, 1941, 1961, and 1982. They concluded that the apparent increase in lung cancer rates over time may be attributed, in part, to advances in diagnostic precision for discriminating among respiratory diseases (Wells et al.).

Another study was done on necropsy data at the same hospital from 1972 to 1981 (Wells & Feinstein, 1998). The authors found that not only were the calculated lung cancer rates after necropsy slightly higher for women than for men, but those rates were substantially higher than usually reported rates. This study concluded that autopsy may be a useful means for establishing the difference between the true occurrence rates of a condition and variations stemming from improvement in diagnostic precision (Wells & Feinstein).

A third study, concurring with the previous one, suggested the ability for detection bias to impede lung cancer detection during a person's lifetime (Mc Farlane et al., 1987). An example of such a bias may occur when a certain category of people is deprived of appropriate diagnosis and therapy because they are known not to engage in a certain behavior specific outcome. In this case-control study men who smoked and coughed were 22 times more likely to have a sputum cytology test ordered than were women nonsmoker who did not cough. This type of bias has the potential to provide misleading (excessively high in men versus low in women) lung cancer estimates (Mc Farlane et al.). These differences in diagnostic considerations represent the uncertainty with trying to explain changing lung cancer rates. Next are discussed some additional factors that have the potential to cause lung cancer.

Other Risks Factors for Lung Cancer

Being a nonsmoker does not always exempt a person from contracting lung cancer. Other factors play a role as well. Passive smokers who, regrettably, are involuntarily exposed to environmental tobacco smoke (ETS) may also be diagnosed with lung cancer. Fortunately, their chance of dying from lung cancer is significantly lower than for smokers: male smokers are 22-times more likely compared to female smokers who are 12 times more likely to experience lung cancer death than are nonsmokers (American Cancer Society, 2004).

According to the Environmental Protection agency (EPA), nearly 3,000 lung cancer deaths occur each year in nonsmokers as a result of inhaling ETS. Statistics show that the risk for nonsmoking spouses of smokers for developing lung cancer is 30% greater than that of spouses of nonsmokers. (EPA, 1993)

Lung cancer may also arise from genetic predisposition. A person with a family history of lung cancer may be at greater risk compared to a person who does not have that history. Also, personal history of lung cancer puts a previous lung cancer patient a higher risk of getting another lung cancer. (CDC, 2006)

As people age their chance of contracting lung cancer will increase. Three-fourths of the total lung cancer mortality occurs in patients aged 65 or more. This is most likely because of the risk build-up over time along with the fact that as cells age their ability to repair decreases (CDC, 2006).

Exposure to carcinogens such as chromium, asbestos, arsenic, vinyl chloride, nickel chromates, coal products, mustard gas and chloromethyl ethers among others in work premises may also make a person at greater risk of lung cancer (CDC, 2006).

Radon is another risk factor for lung cancer. Radon represents another hazardous occupational exposure to lung cancer, e.g., uranium miners. If it is released indoors, it may also cause lung cancer (CDC, 2006).

Fruit and vegetable consumption may have a protective effect on the risk of lung cancer, although this benefit is smaller in comparison to the adverse effects of smoking for lung cancer (CDC, 2006).

Socioeconomic status also contributes to a person's risk of having lung cancer. People who are socioeconomically deprived tend to engage in smoking more commonly; this makes lung cancer rates two to three times higher for this group than people with a better financial situation. (Mao et al., 2001)

Lung Cancer Defined

Lung cancer is a disease of the cells that make up the lungs, the bronchi, or the trachea. It is important to differentiate between lung cancer that originates in the lungs versus cancer that metastasizes to the lung: the former is called primary lung cancer and the latter secondary lung cancer. For instance, a cancer may metastasize to the lung from the breast, bowel, or from another body part. It is very crucial to determine the original site of each cancer case because the choice of treatment is dependent upon the initial cancer site (American Lung Association, 2006).

Types of Lung Cancer

Primary lung cancer can be divided into two main types: non-small cell lung cancers (NSCLC) for which smoking constitute the main cause and small cell lung cancer (SCLC). The categorization is not only based on the main risk factor but the size and the appearance of the cancerous cells. This distinction is also very crucial for the clinical management and prognosis of the disease outcome. NSCLC and SCLC are both primary site cancers. SCLC constitutes nearly 20 % of lung cancer incidence. This type is so called simply for the reason that cancer cells are remarkably small. These cancerous cells are known to spread at their early stage; this will often result in chemotherapy as the final course of care rather than a more complicated treatment method, such as surgery. Smoking is the main risk factor for SCLC; non-smokers would rarely develop it (American Lung Association, 2006).

NSCLC accounts for 80 % of all lung cancer cases. NSCLC can be further classified into three different subtypes. Squamous cell carcinoma comprises about 25% to 30 % of all lung cancers. They are linked to smoking and are likely found near the bronchus. Adenocarcinoma constitutes nearly 40% of all lung cancers. It tends to be found in the outer part of the lung.

Large cell carcinoma constitutes 10% to 15% of all lung cancers. It usually grows and spread more rapidly and can start in any part of the lung. Squamous lung cancer is the most common type of lung cancer and is often caused by smoking. All NSCLC behave in a similar way and they respond to treatment differently than SCLC. The prognosis and management for this class of lung cancer are almost identical (American Lung Association, 2006).

Lung Cancer Symptoms and Diagnosis

Symptoms of lung cancer include persistent cough or a cough that worsens with time, shortness of breath, wheezing or hoarseness, constant chest pain, recurrent chest infection such as pneumonia and bronchitis, coughing up blood, swelling of the neck and face, and unexplained loss of appetite and weight. It should be noted that these symptoms may also be caused by other conditions. Lung cancer may be diagnosed through a series of exams ranging from physical exam of the lung, sputum cytology, bronchoscopy, chest x-rays, special imaging techniques, such as CT scans or MRIs, and lung biopsy (American Lung Association, 2006).

Lung cancer is a chronic disease. In other words, it will take many years, generally ranging from 10 to 40 years, for a person to develop the disease. Symptoms will not start appearing until the tumor has grown to a more crucial or life-threatening stage. For most cancers, surgery is the preferred procedure that may be administered to the patients newly diagnosed. Yet, this is not the case for lung cancer, the stage of disease is generally advanced at the time of diagnosis. Radiation is not an option, as the lungs are too sensitive for the radiation insult. Chemotherapy then becomes the most viable, although limited, option. There is high risk involved with the surgical treatment option because statistics have shown that only 10 % of all cases at this stage are cured (American Lung Association, 2006).

Lung Cancer Prevention

Preventive measures for lung cancer include smoking abstinence and avoidance of second hand smoke inhalation. For occupational exposures related to lung cancer risk, reducing exposure to cancer-causing chemical agents in the work environment is critical (American Lung Association, 2006). Federal laws prescribe the use of respirators and wearing of protective clothing as two of these work-place measures. A well-balanced diet rich in fresh fruits and vegetables may also be protective against lung cancer in both smokers and non-smokers. Vitamin A has been recognized as a protective factor for lung cancer risk (Alavanja et al., 1995).

CHAPTER 3

METHODS

Hypotheses

The goal of this analysis is to assess whether rising rates of lung cancer in Kentucky are a reflection of diminishing rates of emphysema and COPD. The null hypothesis is that COPD and emphysema maps would not vary for those regions shown to be high for lung cancer. The alternative hypothesis is that COPD and emphysema maps will vary for those regions shown to be high for lung cancer. As the thesis title indicates and the literature review discusses, rural poor persons dying of a respiratory disease may be erroneously assigned to the cause of death. This study endeavors to assess the rate of that error called misclassification for these three causes of death. If the rates for two diseases increase, this suggests that there is not an error of classification being made. If rates for one disease increase while those for the other disease decrease, this suggests that the one rising contains death that was misclassified for the disease that was going down.

Data Source and Study Population

Vital data for white males were obtained for the 24-year time period (1979 to 2002) from the National Center for Health Statistics webpage (CDC Wonder, 2005). This race-gender group was selected because minorities represent a very small proportion of the Kentucky population, and male rates were much higher than for females over this time period.

The 24-year time period was divided into 5-year intervals (1979-1983, 1984-1988, 1989-1993, 1994-1998) except for the concluding one (1999-2002) to agree closely with the time periods on lung cancer maps (1950 – 1969, 1985 – 1989, 1990 – 1994) that were at our disposal.

As shown in Table 1, we used the International Classification of Diseases (ICD) codes to compute death rates as the number of deaths per 100,000 population. We then age-adjusted the rates to the 2000 US standard population by using 5-year intervals and summarized by county.

Table 1

International Classification of Diseases (ICD) Codes for Lung Cancer, COPD, and Emphysema

	International Classification of Diseases (ICD) codes	
Diseases	1999 – 2003	1979 – 1998
Lung Cancer	C34 to C34.9	162 to 162.9
COPD	J44 to J44.9	490 to 496.9
Emphysema	J43 to J43.9	492 to 492.9

Map Building

The maps for data presentation were constructed using Microsoft Paint Brush. The shadings on the maps reflect rate categories. These gradients were based on: a rate being below the Kentucky mortality rates for “very low”; Kentucky mortality rates + 1 standard deviation for “low”; Kentucky mortality rates + 2 standard deviation for “moderate”; and > 2 standard deviation of the Kentucky mortality rates for “high”.

Kentucky mortality rates were different for each time period as shown in Table 2.

Table 2

Kentucky State Rates for Lung Cancer, COPD, and Emphysema by Time Interval

	State (Kentucky) rates by time interval	
Diseases	1999 – 2003	1979 - 1998
Lung Cancer	114	177.8
COPD	65.9	59.2
Emphysema	9.5	9.8

Each category was determined based on the standard error of the the Kentucky mortality rates (Hardy et al., 1990). For instance, lung cancer Kentucky rate for the time period of 1993 through 1998 was 117.8 per 100,000. Counties with lung cancer rates below 117.8 were categorized as “very low”. In order to get the values for the “low” category we took the square root of state rate (117.8) to obtain the standard error (10.85). These two numbers were then added together to obtain 128.65. Counties in the “low” category were those with rates between 117.8 and 128.65. The upper boundry of the previous category became the lower boundry of the next. So each time we added the standard error to the upper boundry of the next category to determine the lower boundry of that interval (Hardy et al.; Frumkin & Kantrowitz, 1987).

Data Analysis

Pearson (rates) and Spearman (rank) correlations were performed in Excel to determine the proportion of variation in the dependent measure (lung cancer, for instance) because of the independent variable (emphysema mortality rates, for example). Correlation coefficients and p values were reported and used for interpretation. All interpretations were at $p < 0.05$ level. Lag intervals (for instance, COPD for one time period versus lung cancer for a following time period) were also assessed.

A study of the spatial variation for COPD and for Emphysema was done; this was next compared these to race-gender specific rates for lung cancer, by 5-year time periods and county of residence. The goal was to find out whether rising rates of lung cancer in Kentucky were a reflection of diminishing rates of emphysema and COPD.

CHAPTER 4

RESULTS

Kentucky is a state comprised of 120 counties. This section highlights the geographic trends in lung cancer, COPD, and emphysema mortality across the state from 1989 to 2002.

Figure 3 shows that there are 16 counties with high rates of lung cancer between 1989 and 1993. Half of these counties are clustered in the South Eastern Appalachian region of the state. This is the case for Letcher, for instance, which holds the highest lung cancer rate of 191.3 per 100,000. Appalachia is known for its poverty and coal mining production.

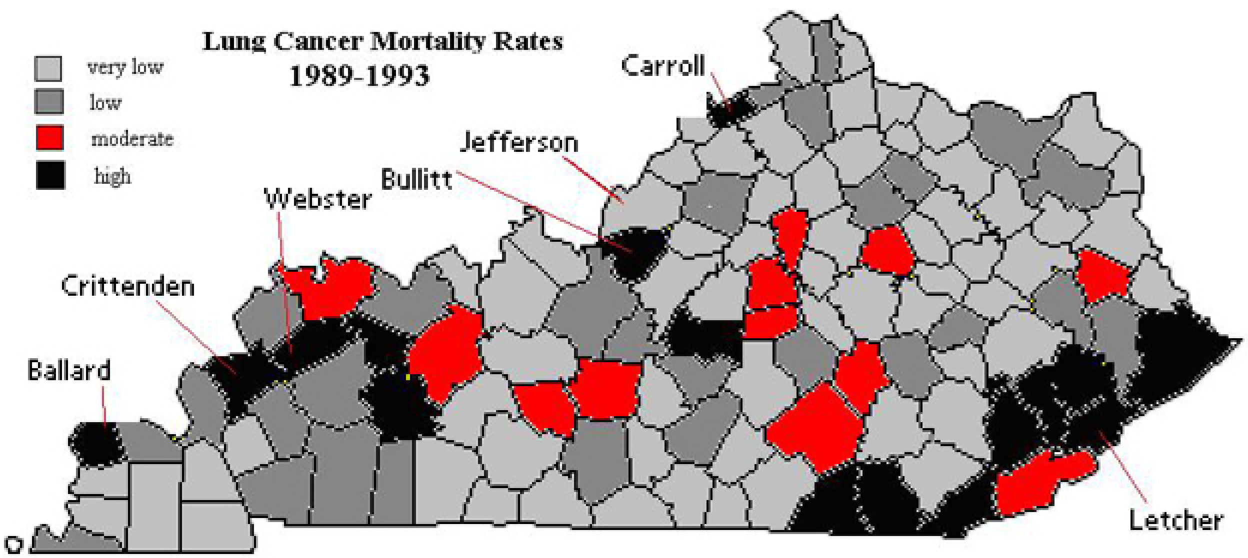

Figure 3. Kentucky Lung Cancer Mortality Rates 1989-1993.

In Western Kentucky there are five counties with high lung cancer rates shaded as being high. These counties are a part of the region shown on the national map as being shaded high as well. These counties are also located west of Jefferson County, the upper center of the state, location of the largest city, Louisville, Also, these rates concur with the high smoking rates [see Appendix A]. They are west of the radon area for the state. Among the five western counties two (Crittenden and Webster) are high for lung cancer are also high for COPD and Emphysema. Ballard is located east of an area where toxic release is high. It is also high in COPD. Bullitt is not only high in radon, but it also lies between two counties where radon and toxic release are high. This county also has high rates of COPD. Further north, Carroll County is in an area with moderate radon and toxic release; this is a part of the suburban region around Cincinnati.

In Figure 4 Kentucky has 58 counties with high COPD mortality rates compared to only 17 counties with high lung cancer rates for the same time period. This is a three-fold frequency of statistically significantly high rates. Most of these counties with high COPD mortality rates are in Appalachia. 12 counties have high rates of lung cancer and COPD in the state. Examples for very high rates in Appalachia are Pike and Letcher counties.

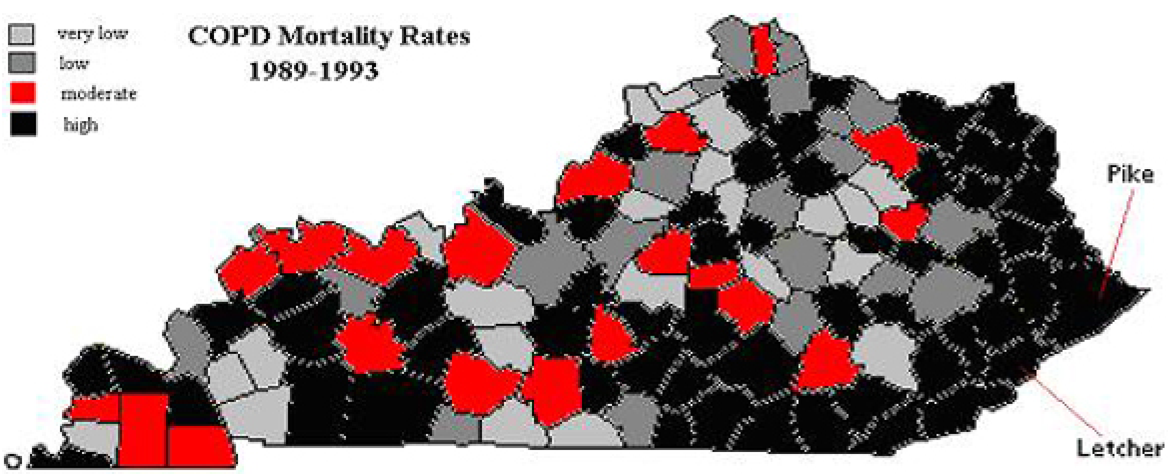

Figure 4. COPD Mortality Rates: 1989 -1993

For this time period we can conclude that there is a very pronounced discrepancy between the number of counties with high COPD and high lung cancer mortality rates for the state (58 vs. 17).

The Pearson Correlation Coefficient (r) here is 0.302. The P value is less than 0.05. This suggests a direct positive correlation between lung cancer mortality rates and COPD mortality rates for the period 1989 through 1993. This means that both continuous measures vary in the same direction, or as mortality rates for lung cancer increase so do those for COPD. One may conclude that there is no evidence of misclassification unless it is for both lung cancer and COPD for this time period because the direction of the relationship is positive.

Figure 5 shows that 19 counties have high rates of emphysema compared to 17 counties with high lung cancer rates. Among those, four are found to be high on both variables: Letcher and Bell in the East and Crittenden and Webster in the West. Lung cancer and Emphysema seem to have dissimilar patterns of mortality in the state in that most of the counties do not have high rates of mortality for both variables. Also, the counties with high rates of Emphysema are scattered throughout the state.

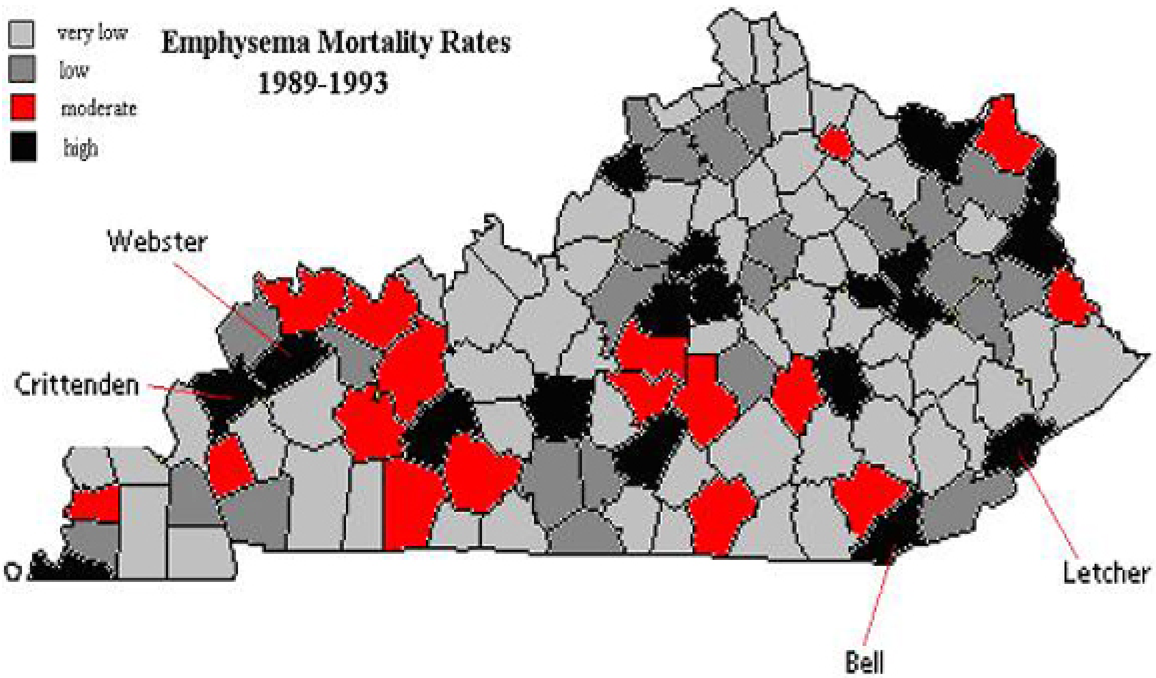

Figure 5. Emphysema Mortality Rates: 1989 -1993

There is a negative Correlation Coefficient for this association: r = -0.009 and a P value greater than 0.05. This suggests a negligible to no relationship between lung cancer and emphysema. Variables vary in opposite direction. A negative sign is evidence for misclassification. However, because the correlation coefficient is very low here, making such a statement would be misleading.

As shown in Figure 6 the number of counties with high rates of lung cancer increased from 12 in 1989-1993 to 24 in 1994-1998. What is interesting is that only six of the counties that had high rates from 1989 through 1993 maintained their high rates in this period. Although half of the counties having high rates of lung cancer death are located in the Appalachia region of Kentucky, as it was the case in the previous period, they no longer are concentrated in the

Southeast as in the previous period. They are scattered throughout the region instead. Seven new counties became high in Appalachia where coal mining and poverty are present. In the North, four new counties: Gallatin, Grant, Bracken, and Mason became high for lung cancer; Pendleton, which is a high radon zone, lies in the middle of these counties. Also above Gallatin and Grant is a county (Boone) which is high in toxic release.

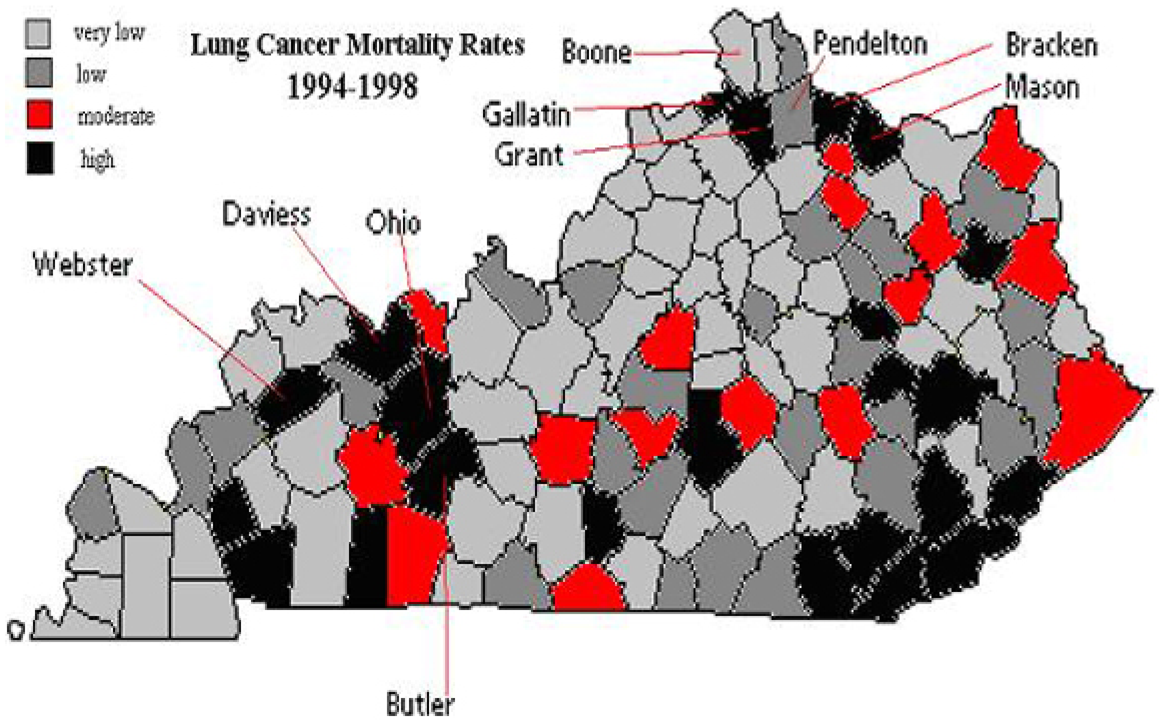

Figure 6. Lung Cancer Mortality Rates: 1994 -1998

In the Northwest part of Kentucky four new counties: Daviess, Ohio, Webster, and Butler are located east of the coal mining area. Daviess is also high in toxic release and the two other counties lie between counties where toxic release is high.

Daviess, Webster, and Ohio are also areas of high smoking based on the 2001 smoking prevalence in Kentucky. However, we cannot state that their high lung cancer mortality rates result from smoking for that year because of the number of years proposed for latency between cigarette consumption and lung cancer diagnosis.

Figure 7 shows that Kentucky has somewhat maintained its number of counties with high rates of COPD mortality which went from 58 to 57 counties. This is contrary to the change for lung cancer death rates that increased from the previous period to this one. Among the counties that have high rates of lung cancer and COPD in the state, 15 are found to be high on both variables.

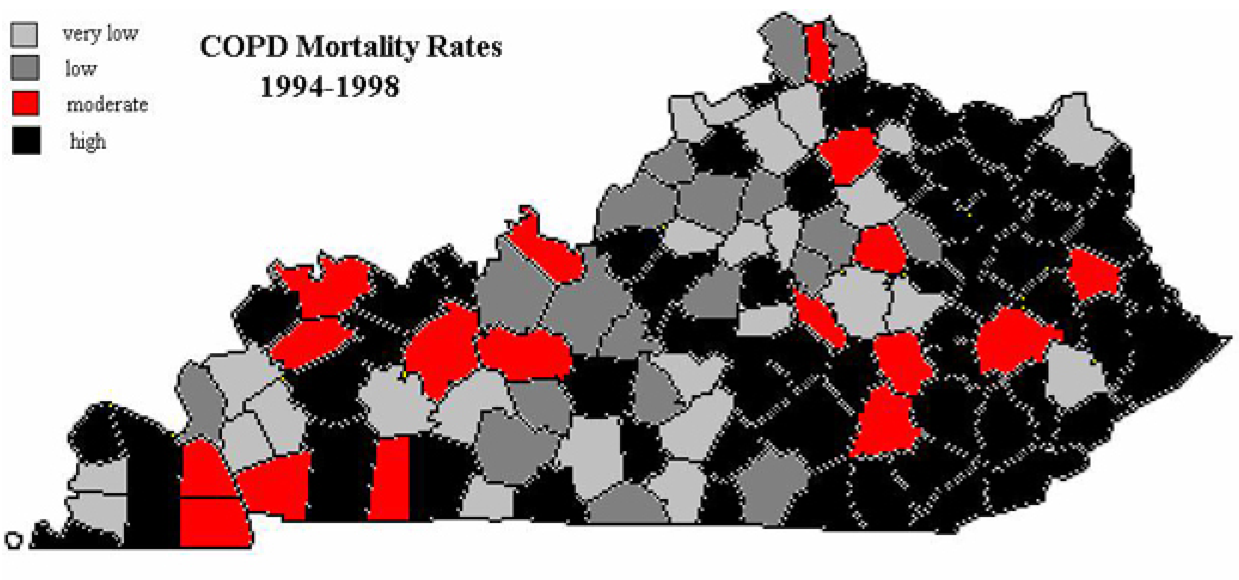

Figure 7. COPD Mortality Rates: 1994 -1998

The Pearson Correlation Coefficient (r) here is 0.196 with a statistically significant P value. Although the correlation between lung cancer and COPD has decreased in magnitude since the previous time period, there is still a direct positive correlation between both variables for the time period of 1994 through 1998. This means that both continuous measures vary in the same direction, or else, as mortality rates for lung cancer increase, so do those for COPD. One may conclude that there is no evidence of misclassification between both lung cancer and COPD for this time period as the direction of the relationship is positive.

Figure 8 shows that the state maintained its number of counties with high rates of emphysema (n = 19). Among the counties that have high mortality rates for lung cancer (n = 24) and Emphysema in the state, three are found to be high on both variables.

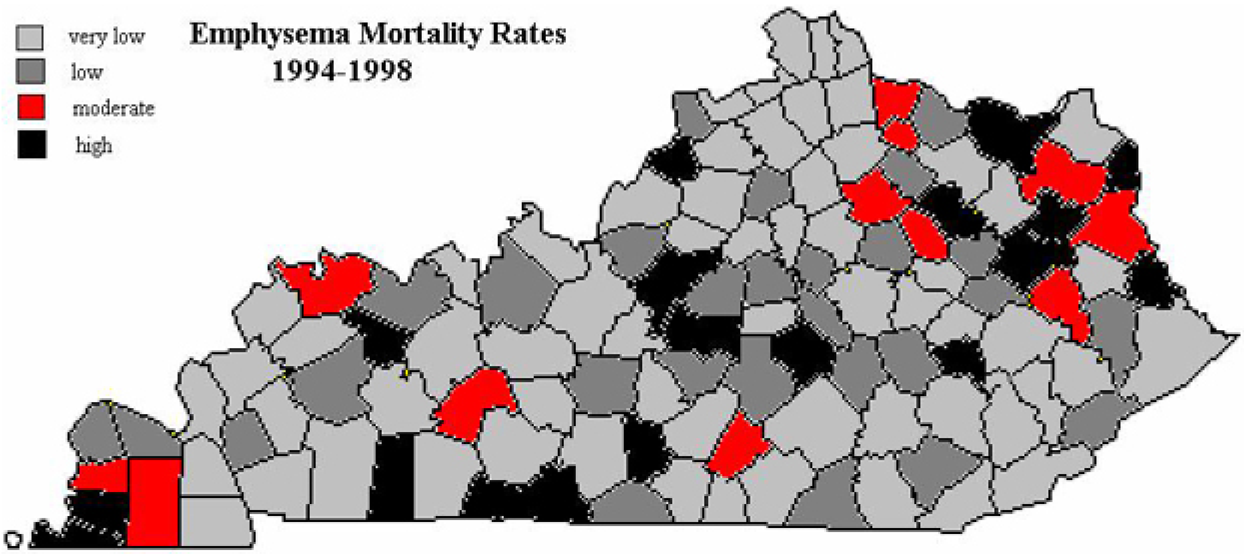

Figure 8. Emphysema Mortality Rates: 1994 -1998

Again there is a negative correlation coefficient for this association between lung cancer and emphysema (r = -0.103) with a non-statistically significant P value. This means that again there is a negligible negative relationship between lung cancer and emphysema. In other words, both variables vary in opposite direction: as lung cancer death rates increase, emphysema mortality rates diminish. Although the correlation coefficient in negative, it is not large enough to suggest a potential misclassification between lung cancer and emphysema death rates for this time period.

Figure 9 shows that the number of counties with high rates of lung cancer increased from 24 to 29 for these years. Of these 18 are located in the Appalachian region of Kentucky. This is the period of time when Kentucky is entirely shaded as having the highest lung cancer mortality rate on the national maps (see Appendix A), e.g., as the dubious leader of the nation in this regard.

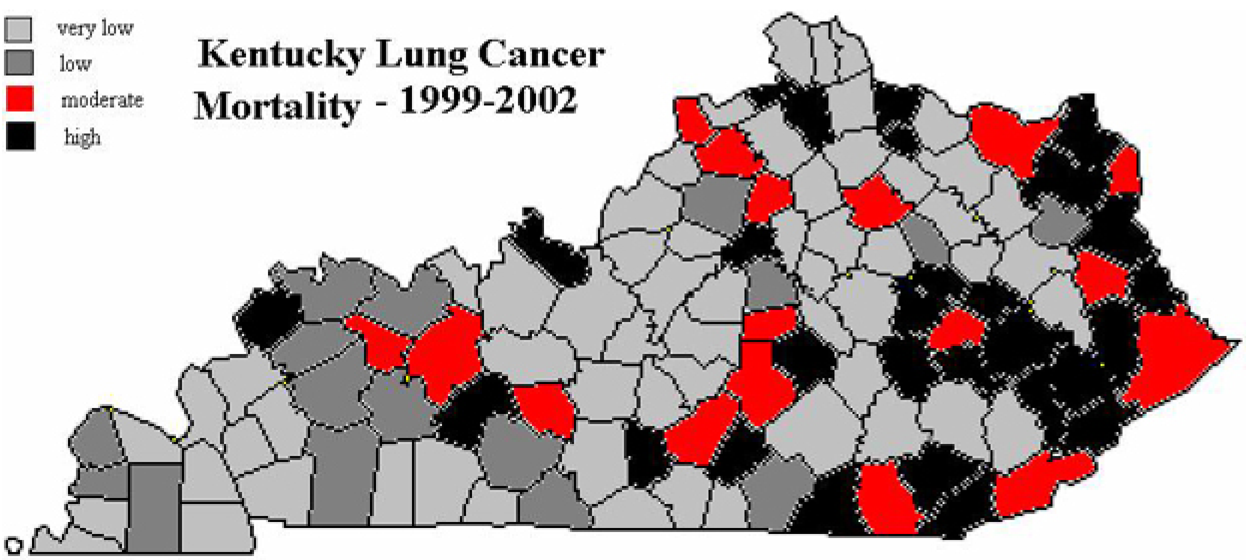

Figure 9. Kentucky Lung Cancer Mortality Rates: 1999 -2002

Based on Figure 10 between 1999 and 2003, 12 counties in total are shaded high in smoking prevalence in Kentucky, compared to the Kentucky statewide rate. Most of these ‘high’ smoking counties (8 counties) are from the Appalachian part of the state. Owing to the state's number one rank in the nation for smoking prevalence there have been a variety of public health campaigns targeting smoking cessation.

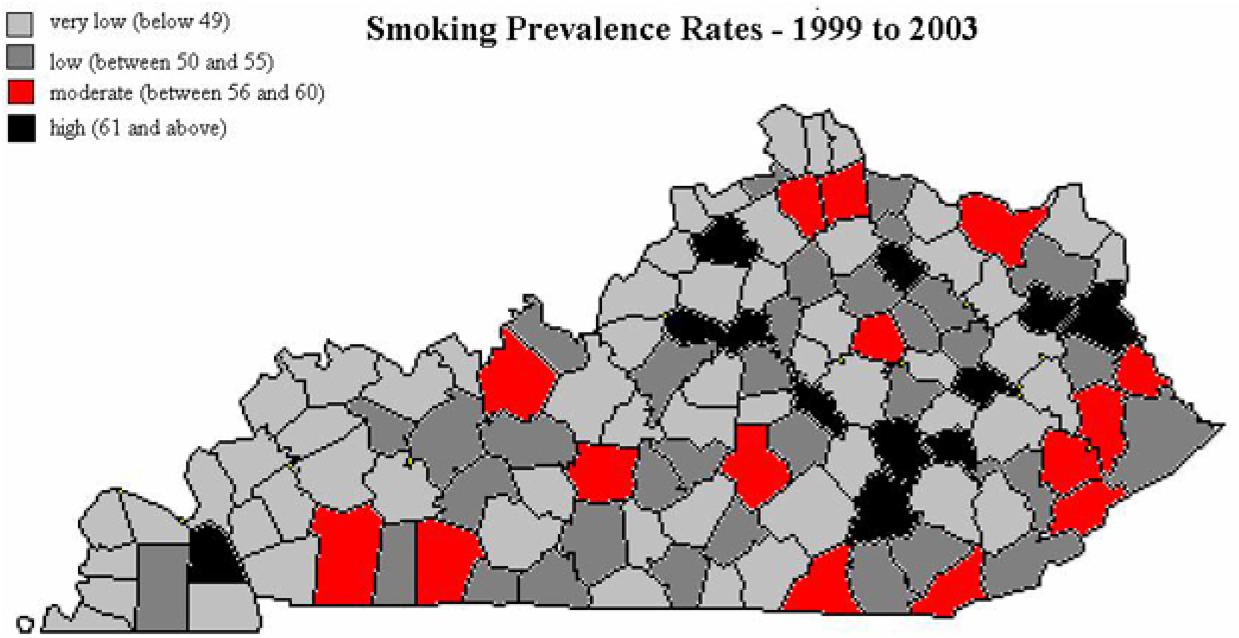

Figure 10. Kentucky Smoking Prevalence:1999 - 2003

The Pearson correlation coefficient between smoking prevalence rates for the period of 1999 through 2003 and lung cancer mortality rates between 1999 and 2002 is 0.15. Although high smoking prevalence correlates with high lung cancer mortality rates, the p-value is not statistically significant. On the contrary, Spearman correlation coefficient for both variables in the same time periods yielded a statistical significant p-value with a coefficient of greater in magnitude: 0.21.

In Figure 11 there is a sharp decrease in the number of counties with high rates of COPD mortality. Among the counties that have high rates of lung cancer and COPD in the state, 10 are found to be high on both variables. There is a pattern for changing rates between lung cancer and COPD. The number of counties with high rates of lung cancer has increased over time from 17 in 1999 to 29 in 2002; on the contrary the number of counties with high rates of COPD has greatly decreased over time from 58 in 1983 to 31 in 2002.

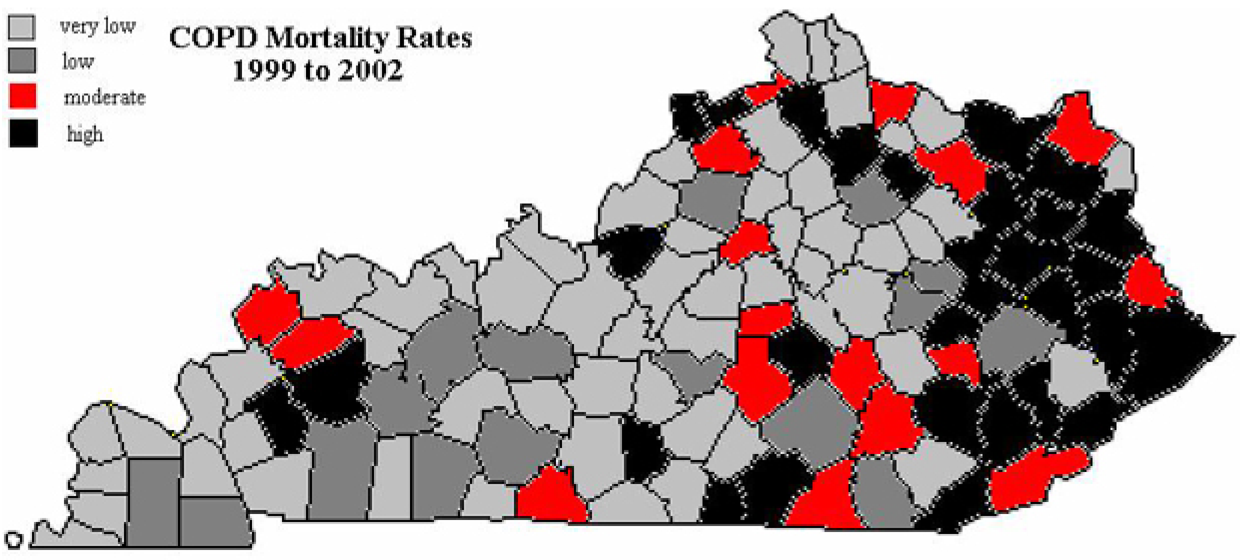

Figure 11. COPD Mortality Rate: 1999 - 2002

The Pearson Correlation Coefficient here is 0.350 with a significant P value. As it was the case in the previous time periods, this suggests a direct positive correlation between lung cancer mortality rates and COPD mortality rates for the time period of 1999 through 2002. In other words, there is no evidence of misclassification because lung cancer and COPD mortality rates increase simultaneously.

In Figure 12 the number of counties with high rates of Emphysema has increased by one, from 19 to 20. Among the counties that had high rates of lung cancer and COPD in the state, seven are found to be high on both variables.

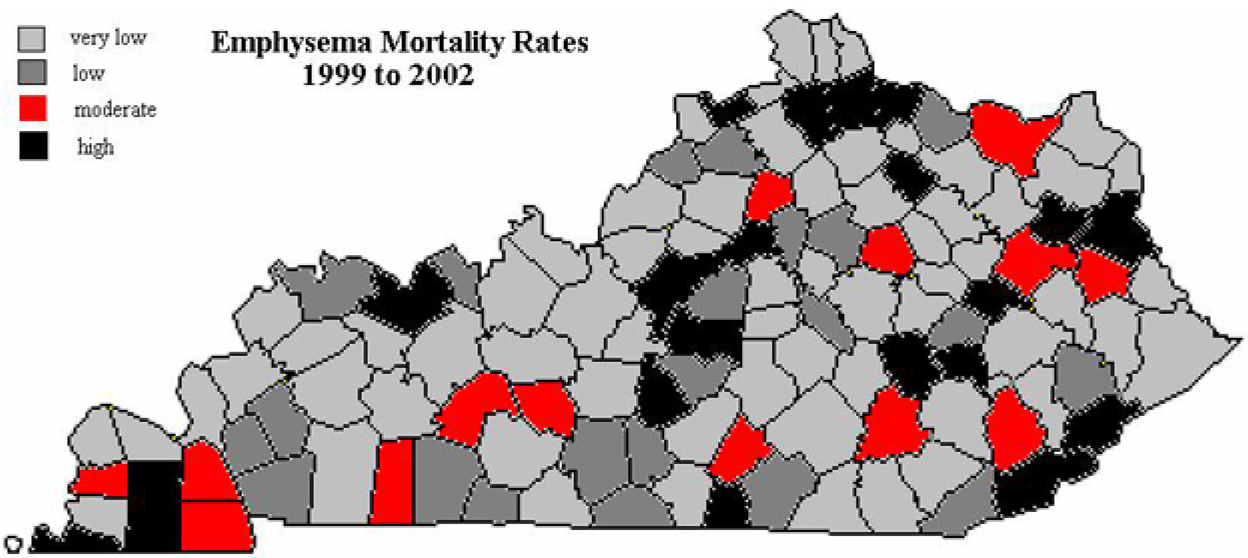

Figure 12. Emphysema Mortality Rates: 1999 - 2002

Unlike in the previous time periods there is no evidence of misclassification for this one; the correlation coefficient for this association between lung cancer and emphysema mortality rates is positive: 0.027 and the P value is not statistically significant. As it was mentioned before the positive sign means that there is a direct relationship between lung cancer and emphysema: both variables behave in the same direction.

Figure 13 depicts the variation for COPD and Emphysema for the sequential, corresponding time period and with the changes over successive time periods from the first five-year time period. Both variables, Emphysema and COPD, did show a decided trend downward, e.g., the line for the same time periods. However, the line representing the 'lag' from earlier to later time periods shows a vacillation in the agreement for which counties were high with the respective diseases over time.

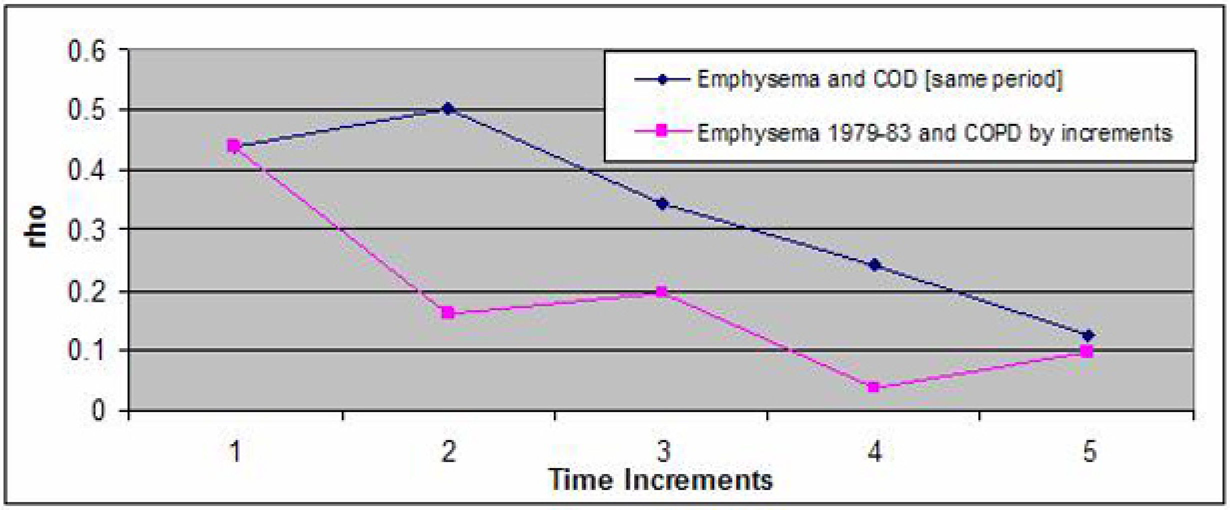

Figure 13. Correlation Between COPD and Emphysema.

A comparison between lung cancer mortality rates from time increment 3 through time increment 5 (e.g. 1989 to1993, 1994 to 1998, and 1999 to 2002) shows that the counties with high lung cancer mortality rates are not always the same from time period to time period. For example, among the counties that had high rates of lung cancer mortality from 1989 to1993 only 7 out of 22 counties maintained high lung cancer mortality rates from 1994 to 1998; those are Bell, Leslie, Letcher, and Whitley for Appalachian Kentucky and McLean, Muhlenberg, and Webster for the non-Appalachian part of the state. From 1999 to 2002 there are 28 counties with high lung cancer mortality rates from which 10 have remained "high" from the previous time period: Bell, Breathitt, Knox, Letcher, Powell, Bracken, Gallatin, Grant, Metcalfe, and Muhlenberg. Only three counties kept their high lung cancer mortality rates throughout the three time periods (1989 to1993, 1994 to 1998, and 1999 to 2002); these are Bell, Letcher, and Muhlenberg.

Also for lung cancer and COPD, counties with high rates for both diseases are not always the same from time period to time period. From 1989 to 1993, 12 counties have high mortality rates of both lung cancer and COPD. Those are Ballard, Crittenden, Webster, and Bullitt for the non-Appalachian part of the state; and McCreary, Whitley, Pike, Letcher, Knott, Leslie, Bell, and Perry for Appalachian Kentucky. From 1994 to 1998 among the 15 counties that have both high rates of lung cancer and COPD mortality only 4 have maintained their high rates from 1989-1993: Letcher, Bell, Leslie, and Whitley and they are all located in Appalachia. For the time period of 1999 through 2002, 10 counties are “high” for COPD and lung cancer mortality rates in the state. Among them only 3 were high from 1993 to 1998: Metcalfe is outside Appalachia while Bell and Letcher are in Appalachia. From 1989 to 1993, 1994 to 1998, and 1999 to 2002 only Bell and Letcher did maintain high mortality rates for both diseases.

These data validate the value of studying the region as the unit of general lung cancer risk. The county level, like the individual level, is simply more variable. Our analysis is sensitive to this individual variability. Regional characteristics like poverty and smoking prevalence would be more stable when studied at the regional level.

CHAPTER 5

DISCUSSION

Overall, the results of this study suggested little evidence of misclassification between the rising lung cancer rates over time in correlation with changing COPD and emphysema mortality rates. Although the correlation coefficients for lung cancer and emphysema remained negative throughout two time periods, they could not be taken into account because of their tiny magnitudes. COPD showed some agreement (e.g., positive correlation) with lung cancer rates. As the lung cancer rates rose, COPD rates rose. Emphysema and COPD did show a decided trend for agreement with rising rates but declining agreement on which counties were 'high.' As well, there was varying pattern for agreement with 'high counties' between COPD and Emphysema applying a 'lag' from the earliest to later time periods.

Three studies were mentioned in the literature review section. These articles posed the most compelling basis for the analyses reported in this thesis. These articles suggested misclassification as an explanation for the continuous rise of lung cancer rates nationally; this thesis examined it for Kentucky. However, all of those analyses were done at the individual level (Wells et al., 1990). This analysis examined that trend for observed spatial trends over time using county-level data. For example, the present study did not review patient records but relied on aggregate rates for a county as a whole. Two other papers examined other aspects of these time trend implications in Kentucky. In 2006 Saad et al. examined the spatial variation for late stage of diagnosis in Kentucky as being related to the deprivation in Appalachia for health services and poverty in general. That same year Aneja reviewed case records on anther topic (bronchioalverlor carcinoma). County level data are vulnerable to biases that are not likely to occur in results originating from individual-level data. This is because relationships between group-level variables do not necessarily reflect those between individual-level variables.

In order to validate these findings, further studies designed to look for statistical correlations using individual data need to be conducted. This is, unfortunately, not easily feasible because of the high cost associated with such studies. Given the very high rates for lung cancer, such studies are deemed necessary because of lung cancer's burden to the society. The findings will help elucidate the reasons behind the increasing lung cancer mortality rates in order to better address this concern.

In the present study no consideration was made for biologic interval. Because of a latency period, as cigarette consumption will decrease, an accompanying consistent decrease in lung cancer mortality rates will not be likely to occur until after more than a decade (about 10 -20 year lag).

Choice of a different time period cut off may also have yielded different results. For instance, if the present study time period was broken into two-year increments, closer variation between counties over time might be seen.

<u>Potential Causes for Elevated Lung Cancer mortality Rates in Kentucky</u>

The fact that our study was not conclusive prompted us to looked into other potential causes for elevated lung cancer mortality rates. Cigarette consumption accounts for nearly 90% of the causes for lung cancer. This leaves the remaining 10% to be explained. One may think that over time there is an accumulation of other factors such as employment with respiratory hazards (e.g., coal production, radon, asbestos, and other carcinogens) as well as interaction among lung cancer risk factors. If this is the case, public health programs might need to also target less exposure to those carcinogens in the battle of lung cancer.

An important feature of the maps is the clustering of high outlier counties in the Appalachian Kentucky. This is a region mainly characterized by poverty. A lower socio-economic status will usually predict smoking behavior, poor diet, high-risk employment (e.g. with exposures to carcinogens), as well as lack of good health care. Coal production is also highly concentrated in this region. The geographical distribution of particulate matters ($PM_{2.5}$) map shows Appalachia Kentucky as highly exposed to $PM_{2.5}$. Epidemiologic evidence supports associations between inhalation of fine particulate matter and increases respiratory morbidity and mortality.

These four variables of poverty, lack of accessibility to health care, $PM_{2.5}$, as well as coal mining production may act synergistically with cigarette consumption to increase high lung cancer rates in Appalachia Kentucky. (Appendix C)

Radon has been found to cause 10% of lung cancer cases (Alberg & Samet, 2003). The EPA Map of Radon Zones shows that the middle part of Kentucky is highly exposed to radon. There is also evidence of Toxic Release from chemical and plastics manufacturing industries located throughout the state of Kentucky. Exposure to these carcinogens is a possible reason for increase lung cancer risk. (Appendix C) Misclassification does not seem to play a predominant role, at least for COPD and emphysema, as far a rising lung cancer rates in Kentucky is concerned. Therefore, the implication is that forces other than cigarette smoking patterns may explain very little of the geographic and temporal trends for lung cancer in Kentucky. Even if misclassification did make a difference, because cigarette smoking is too common, the greatest public health benefit would be to still recommend that people don't smoke in order to save lives.

CHAPTER 6

CONCLUSION

The findings of this study suggested little evidence of misclassification bias between the rising lung cancer rates over time in correlation with changing COPD and emphysema mortality rates. Although the correlation coefficients with lung cancer and emphysema did remain negative throughout two time periods, they could not be taken into account because of their tiny magnitudes. Regrettably, we are left with the implications that forces impacting cigarette smoking patterns (not studied) may be the explanation for the geographic and temporal trends in Kentucky. Interestingly, some of these “very high rate areas” are already showing “declines” in lung cancer since 1995 (e.g., the far western counties of the state).

REFRENCES

1. Alavanja MC. Brownson RC. Benichou J. Swanson C. Boice JD Jr (1995). Attributable risk of lung cancer in lifetime nonsmokers and long-term ex-smokers. Cancer Causes and Control, *6*, 209-16.

2. Alberg AJ., and Samet JM (2003). The Epidemiology of Lung Cancer. American College of Chest Physicians, *123*, 21S-49S.

3. Aneja J. (2006). Bronchioalveolar Carcinoma in Jefferson and McCracken Counties Kentucky: Gender differences in Survival. Master's Thesis in preparation. ETSU.

4. American Cancer Society (2004).Women and Lung Cancer. Accessed on August 10, 2006 at http://www.lungcancer.org/patients/women_lung_cancer/women_lc.htm

5. American Cancer Society. American Cancer Society Report Finds Drop in Total Cancer Deaths (2006). Accessed on May 10, 2006 at http://www.cancer.org/docroot/MED/content/MED_2_1x_American_Cancer_Society_Report_Finds_Drop_in_Total_Cancer_Deaths.asp

6. American Cancer Society (2006). Cancer Statistics. Accessed at http://www.cancer.org/downloads/STT/Cancer_Statistics_2006_Presentation.ppt On August 10, 2006

7. American Lung Association (2006). Facts about Lung Cancer. Accessed at http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=35427

8. Bhatnagar A. Environmental Cardiology: Studying Mechanistic Links Between Pollution and Heart Disease. Circulation Research. 2006; 99(7):692-705. Used by the authors permission. Accessed 5/1/07.
Available at: http://circres.ahajournals.org/cgi/reprint/99/7/692

9. Britanica Online (2006). A social and cultural history of smoking. Accessed on 1/10/2006 at http://www.britannica.com/eb/article-242784/smoking

10. Center for Disease Control and Prevention (2006). Lung Cancer: Risk Factors. Accessed on August 10, 2006 at http://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm

11. CDC Wonder (2005). Compressed Mortality File. Accessed November 10th 2005 http://wonder.cdc.gov/mortSQL.html

12. Frumkin H and Kantrowitz W (1987). Cancer Clusters in the Workplace: An approach to Investigation. J,. Occupational Medicine. *29* 949-52.

13. Hardy R, Schroder G, Cooper S, Buffler P, Prichard H, Crane M. (1990). A surveillance System for Assessing Health Effects from Hazardous Exposures. American J. of Epidemiology. *132* S32-S42. 1990.

14. Healthy People 2010 (2000). Cancer. Accessed at http://www.healthypeople.gov/Document/HTML/Volume1/03Cancer.htm On August 10, 2006

15. Hopenhayen C, Jenkins TM, Petrik J. Lung Cancer in Kentucky (2003). Journal of the Kentucky Medical Association, *101,* 15-20.

16. Kavanagh T. K. (2002). Cigarette Smoking and Lung Cancer Accessed on 3/10/2005 at http://www.tobacco-facts.info/lung_cancer.htm

17. Mao Y, Hu J, Ugnat A. (2001). Socioeconomic Status and Lung cancer Risk in Canada. International Journal of Epidemiology, *30,* 809-817.

18. McFarlane M.J. Feinstein A.R. Wells C.K. Chan CK (1987). The 'Epidemiologic Necropsy'. Unexpected Detections, Demographic Selections, and Changing Rates of Lung Cancer. *The Journal of the American Medical Association, 258,(3),* 331-8.

19. MMWR (1999). Tobacco Use—United States, 1900-1999. Accessed on 1/10/20065 at http://jama.ama-assn.org/cgi/content/full/282/23/2202

20. MMWR (2003). State-Specific Prevalence of Current Cigarette Smoking Among Adults --- United States. Accessed at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5344a2.htm On May 10, 2006

21. MMWR (2004). State-Specific Prevalence of Cigarette Smoking and Quitting Among Adults --- United States. Accessed at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5444a3.htm On August 10, 2006

22. National Cancer Institute. Cancer Mortality Maps and Graphs. Accessed 10/5/2005 at http://www3.cancer.gov/atlasplus/about.html

23. National Center for Health Statistics. Maps for Lung Cancer: Age-adjusted Death Rates by HAS, 1988-92. Accessed 10/5/2005 at http://www.cdc.gov/nchs/data/gis/atmaplc.pdf

24. Saad F, Ravdal H and Aldrich TE. (2006) Unstaged Lung Cancer in Kentucky: Good News. *Journal of the Kentucky Medical Association*. [In Press].

25. Samet J.M. (1993). The Epidemiology of Lung Cancer. American College of Chest Physicians,*103,* 20S-29S.

26. Wells C.K. Chan C.K. Milstone E.B. Pfister D.G. Feinstein A.R. (1990). Diagnostic Criteria and Technology as Sources for Changing Incidences of Pulmonary Diseases. *American Journal of Medicine, 88,(2),*117-22.

27. Wells C.K. Feinstein A.R. (1998). Detection Bias in the Diagnostic Pursuit of Lung Cancer. *American Journal of Epidemiology, 128,(5),*1016-26.

28. MMWR (1999). Tobacco Use—United States, 1900-1999. Accessed on 3/10/2006 at http://jama.ama-assn.org/cgi/content/full/282/23/2202

29. World Health Organization (2006). Cancer. Accessed on May 10 2006 at http://www.who.int/mediacentre/factsheets/fs297/en/index.html

30. Second Hand Smoke. Accessed on August 10, 2006 at http://ehso.com/SmokingEPAFacts.htm

APPENDIX A

U.S. Maps of Cause Specific Mortality

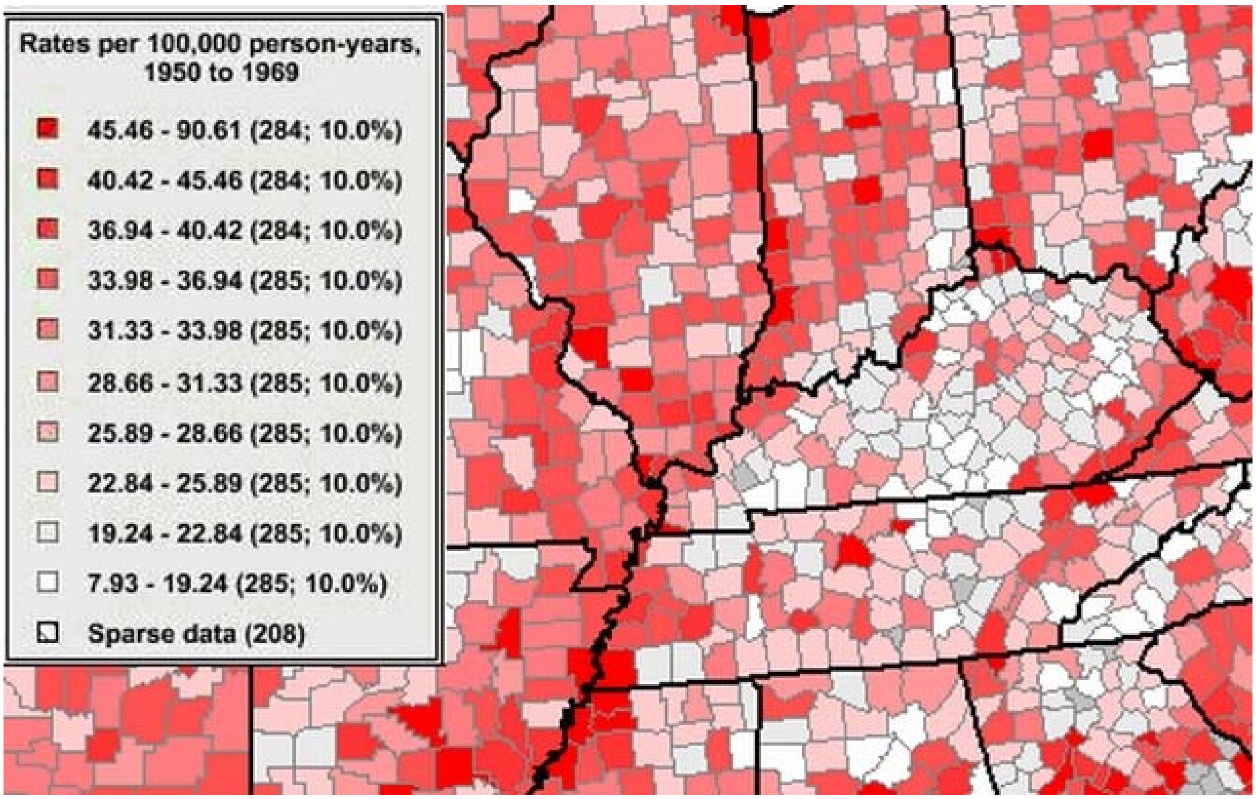

Figure 14. The Increase of Lung Cancer Over Time: 1950 -1969 (22).

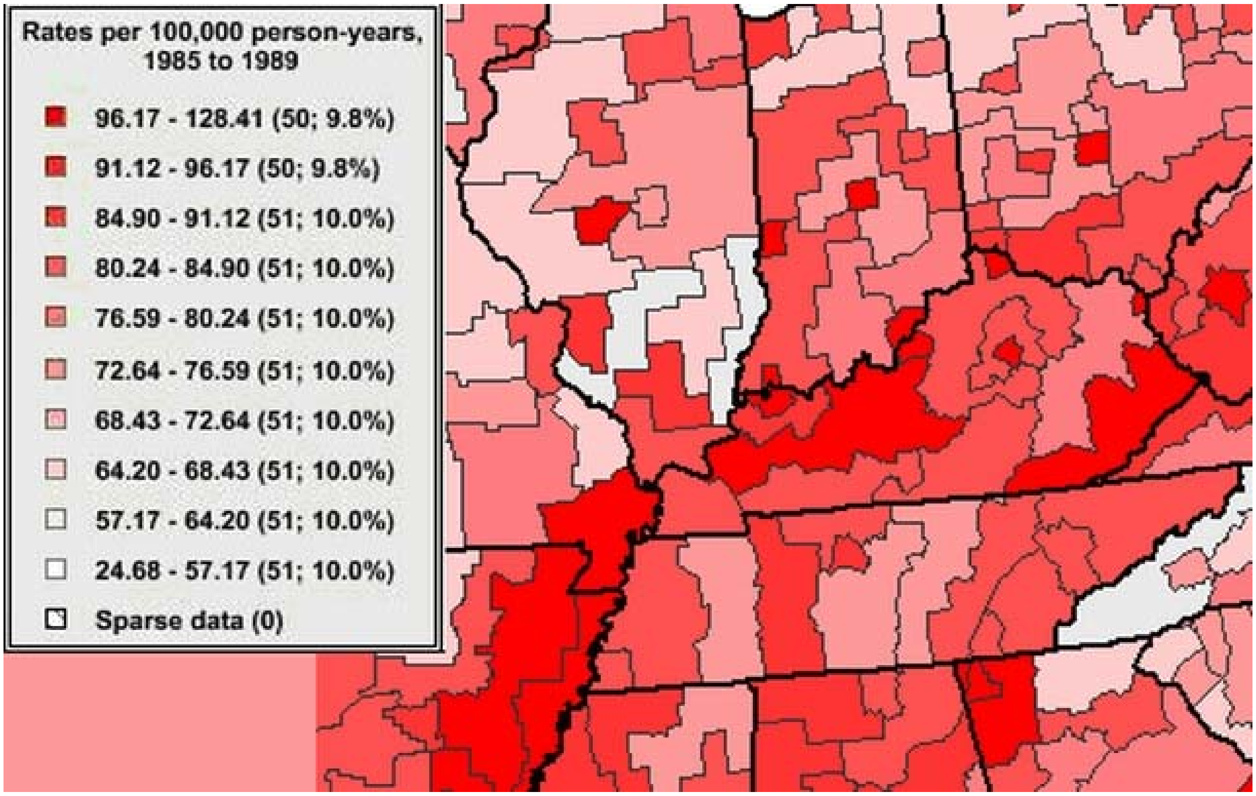

Figure 15. The Increase of Lung Cancer Over Time: 1985-1989 (22).

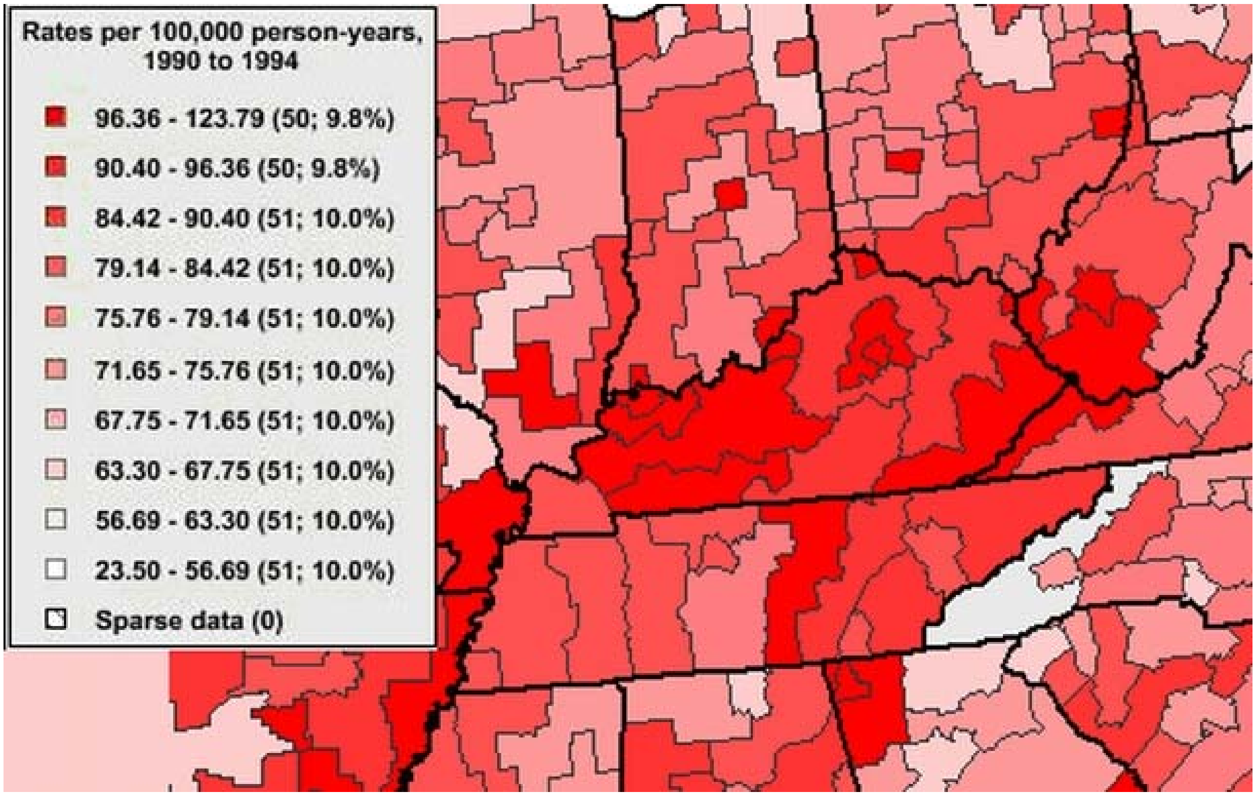

Figure 16. The Increase of Lung Cancer Over Time: 1990 -1994 (22).

APPENDIX B

Other Kentucky Lung Cancer and Related Maps

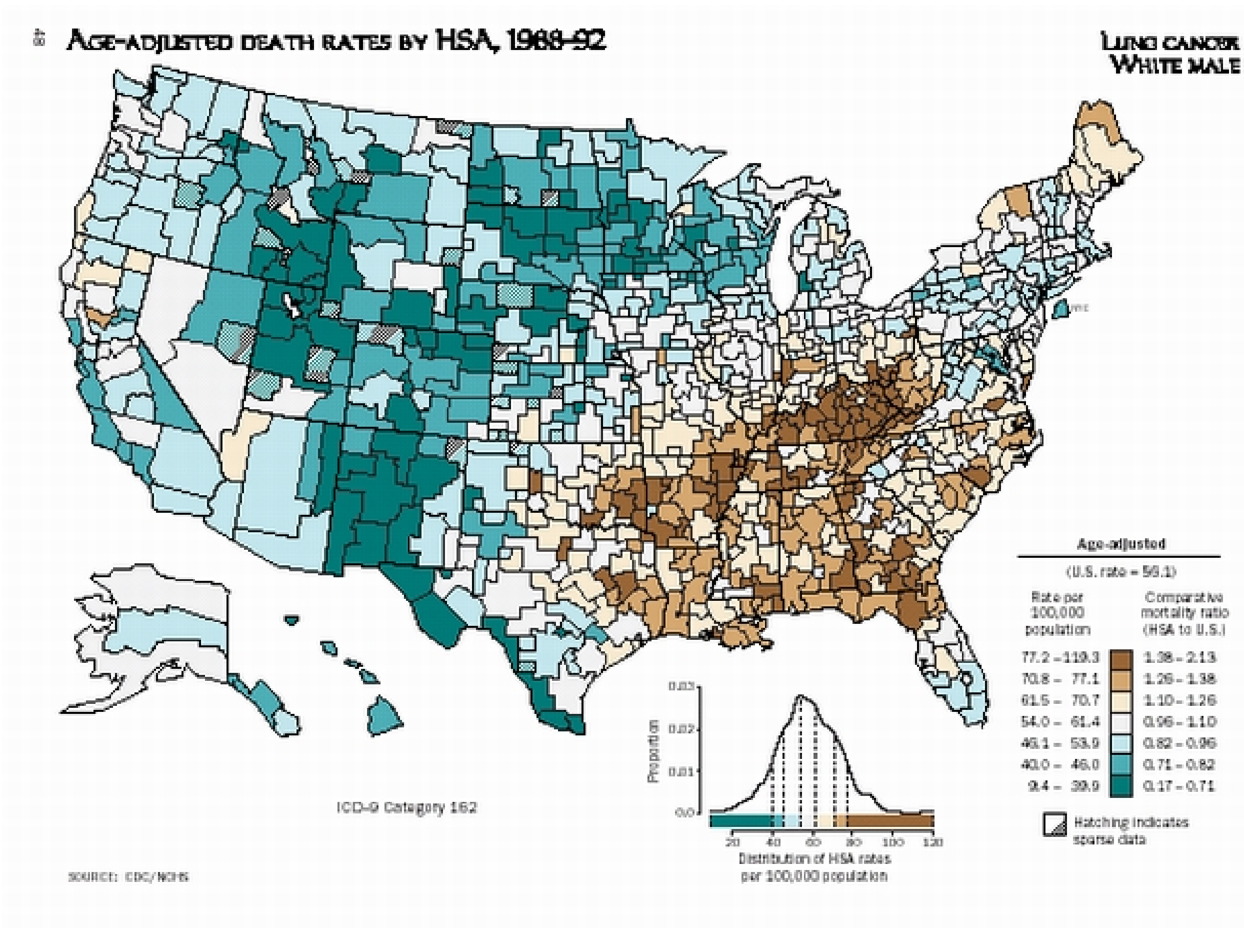

Figure 17. Age-adjusted Death Rates for Lung Cancer for White Males (23).

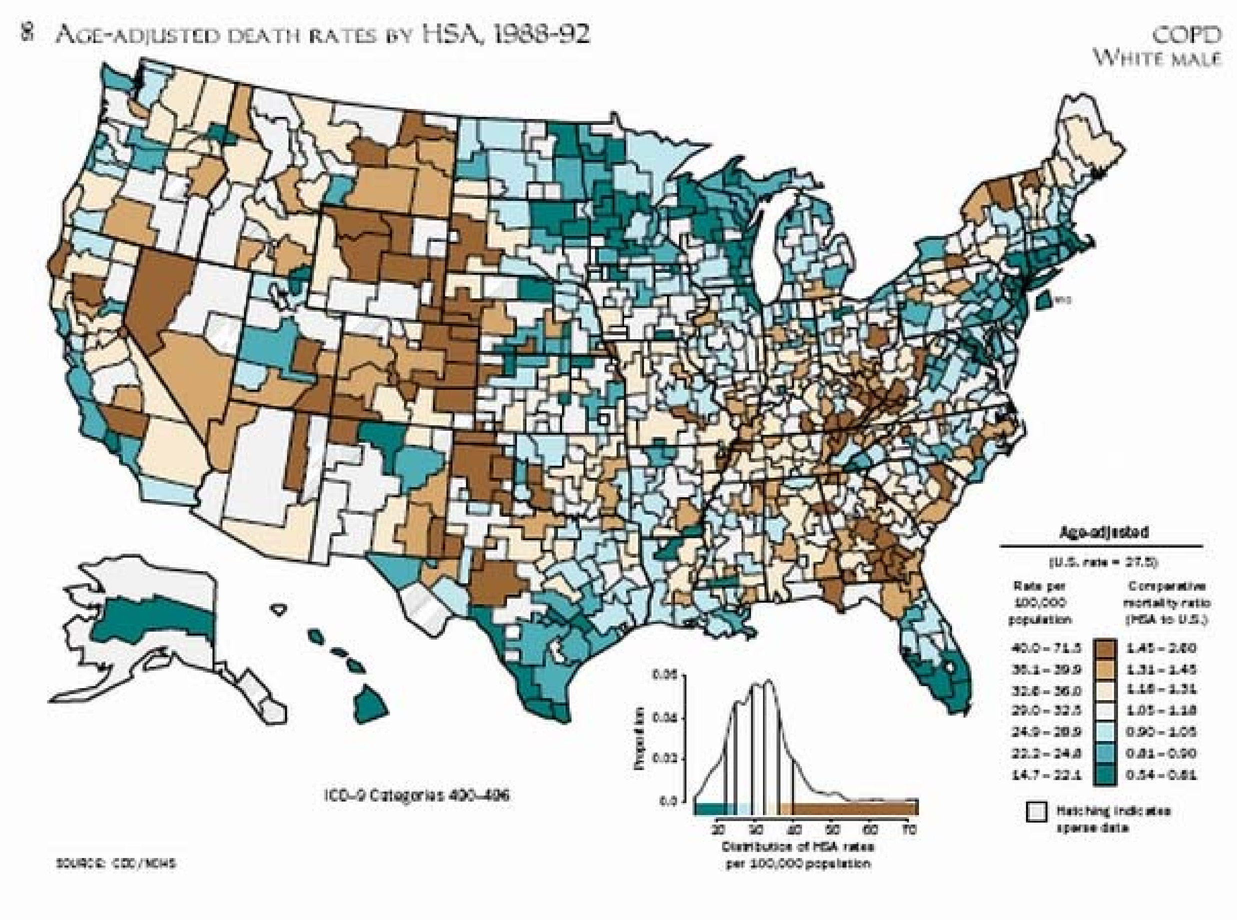

Figure 18. COPD Age-adjusted Death Rates for White Males (23).

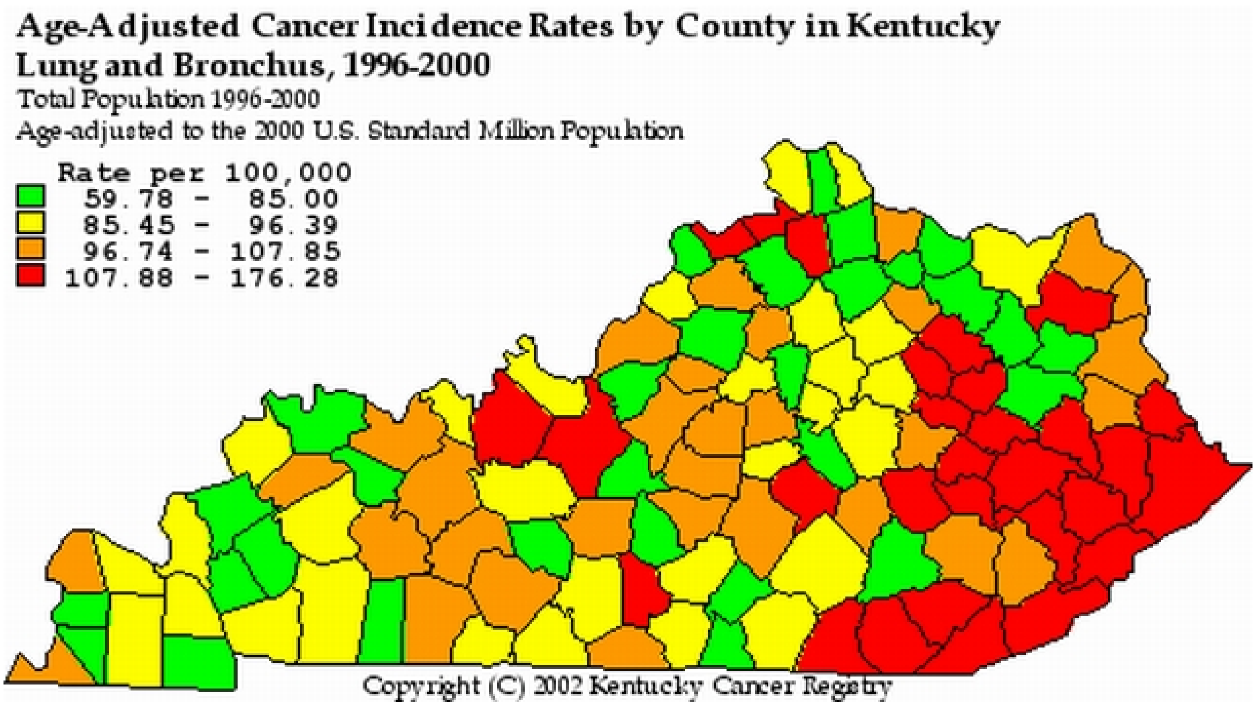

Figure 19. Age-adjusted Cancer Incidence Rates by County in Kentucky (22).

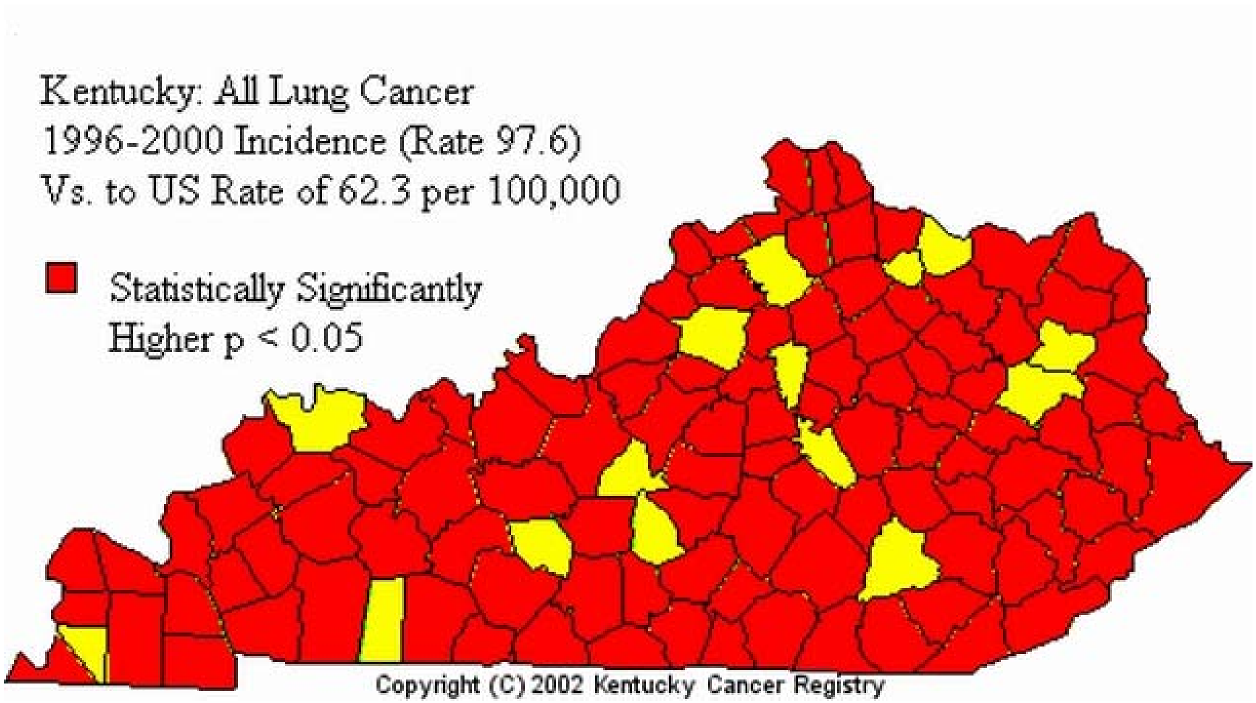

Figure 20. Kentucky: All lung Cancer 1996 – 2000 (22).

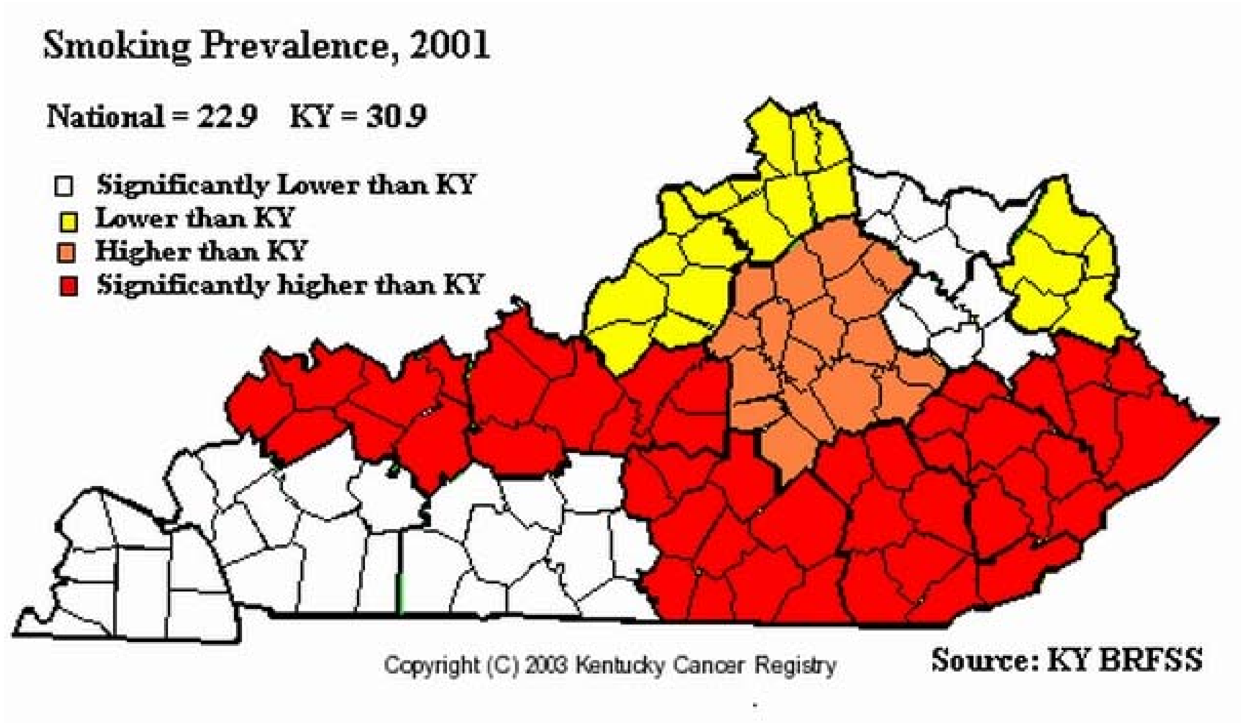

Figure 21. Kentucky Smoking Prevalence (22).

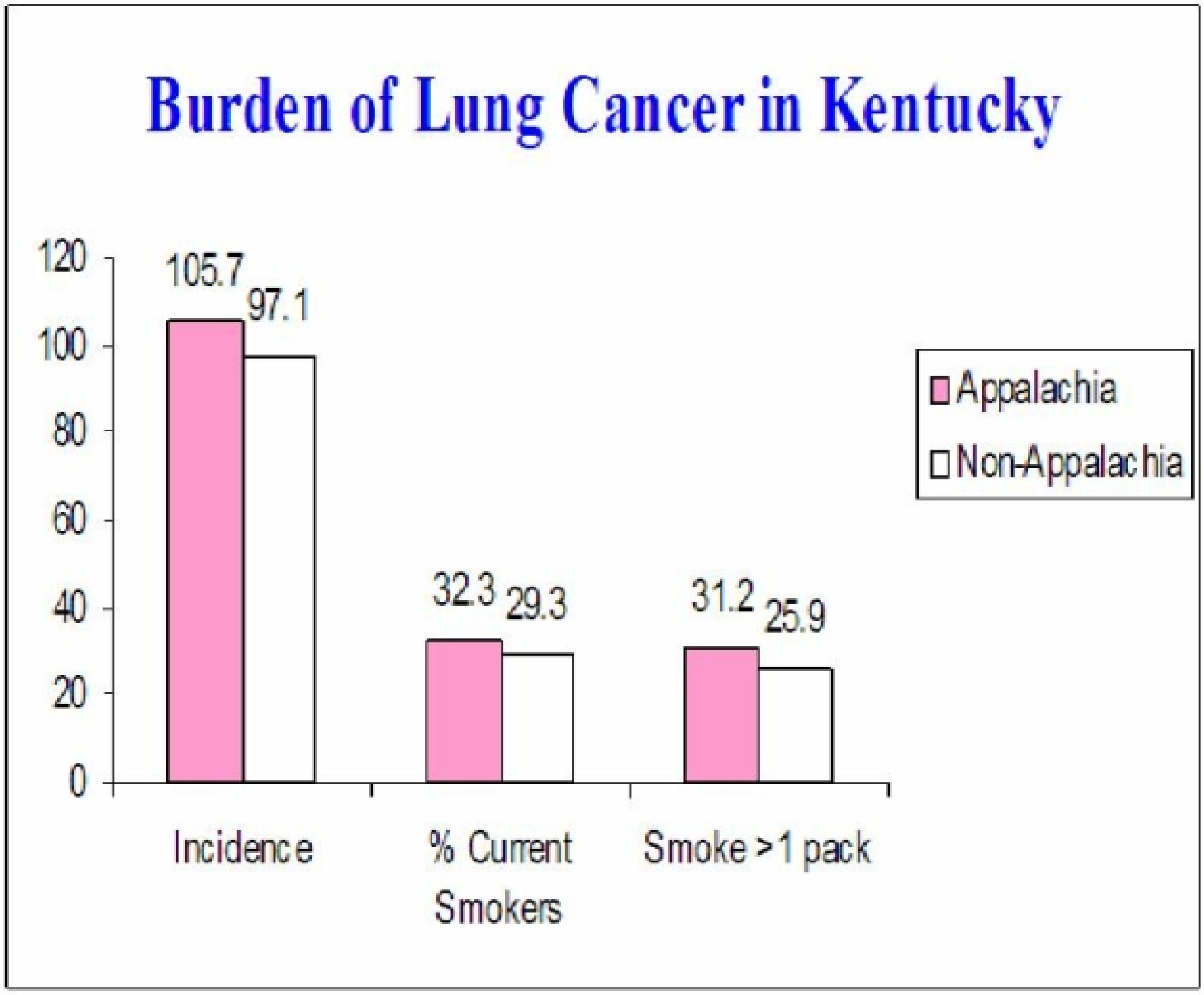

Figure 22. The Burden of Lung Cancer in Kentucky (22).

APPENDIX C

Other Distributions of Possible Lung Cancer Risk Factors in Kentucky

The U.S. EPA and the U.S. Geological Survey have evaluated the radon potential in the U.S. and have developed this map is to assist National, State, and local organizations to target their resources and to assist building code officials in deciding whether radon-resistant features are applicable in new construction. This map is not intended to be used to determine if a home in a given zone should be tested for radon. Homes with elevated levels of radon have been found in all three zones. All homes should be tested regardless of geographic location. The map assigns each of the 3,141 counties in the U.S. to one of three zones based on radon potential. Each zone designation reflects the average short-term radon measurement that can be expected to be measured in a building without the implementation of radon control methods. The radon zone designation of the highest priority is Zone 1.

Zone 1 Highest Potential (greater than 4 pCi/L)

Zone 2 Moderate Potential (from 2 to 4 pCi/L)

Zone 3 Low Potential (less than 2 pCi/L)

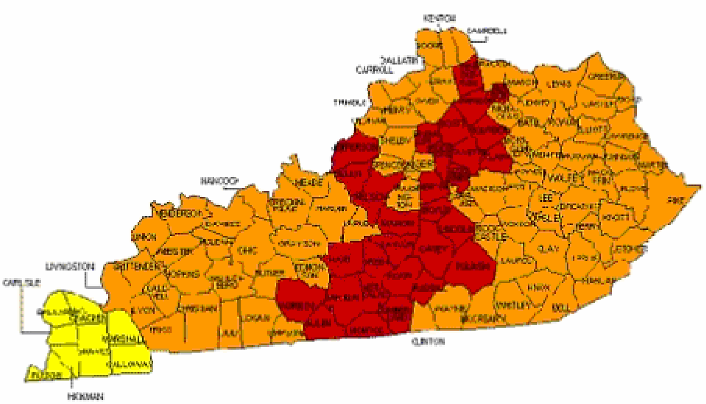

Figure 23. EPA Map of Radon Zones, Kentucky (22).

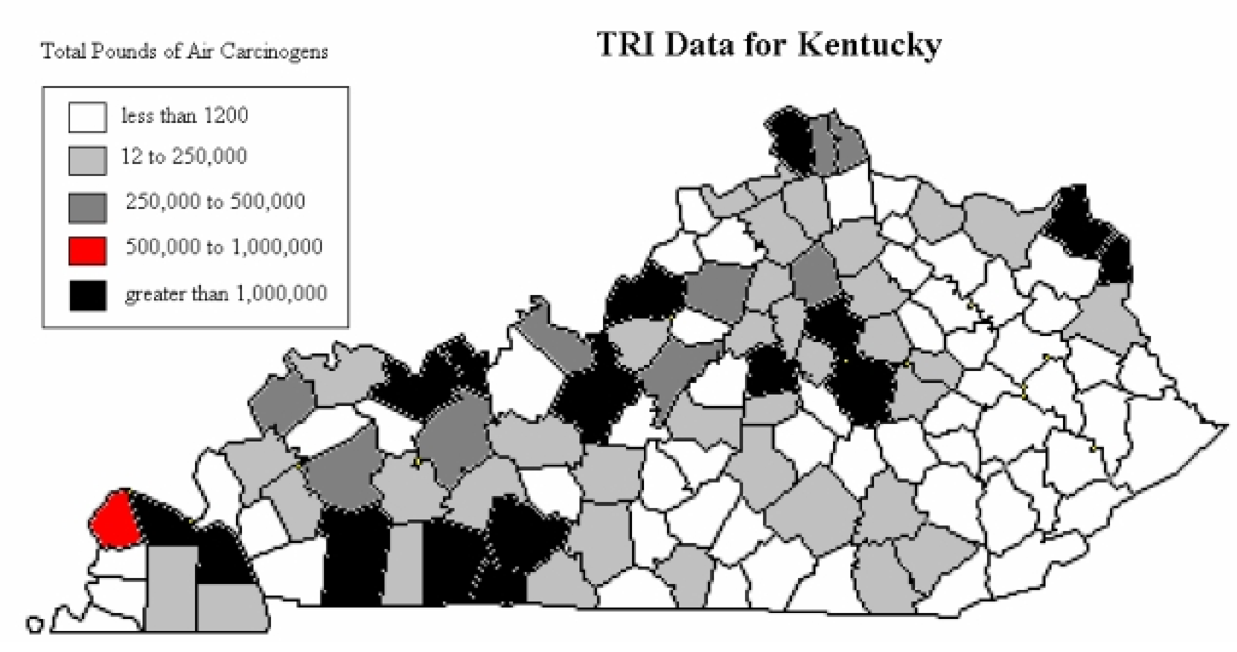

Figure 24. Toxic Release Inventory Data (22).

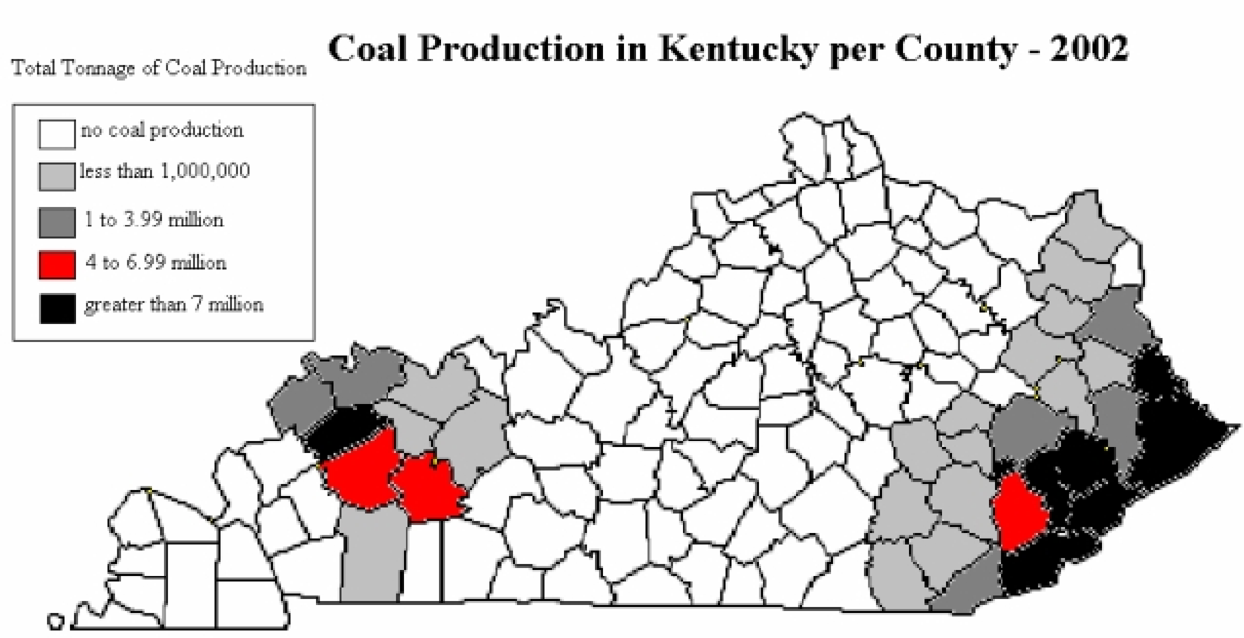

Figure 25. Coal Mining Regions Indicating 'Dirty' Lung Settings in Kentucky (22).

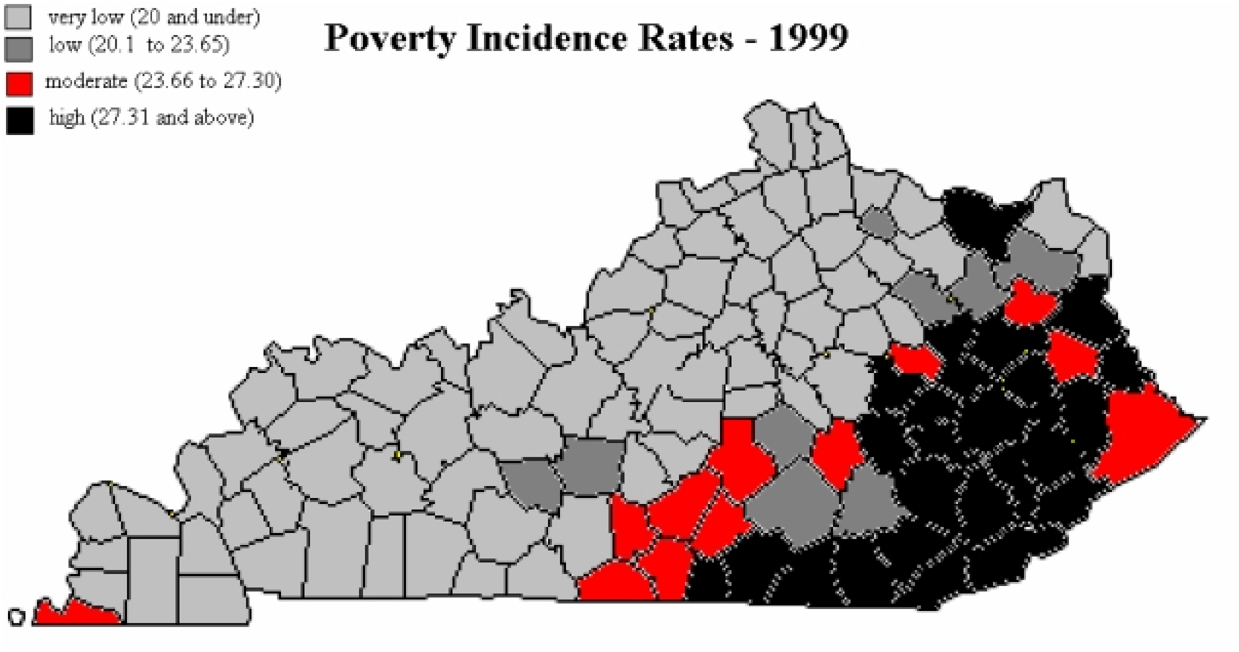

Figure 26. Poverty Distribution in Kentucky (22).

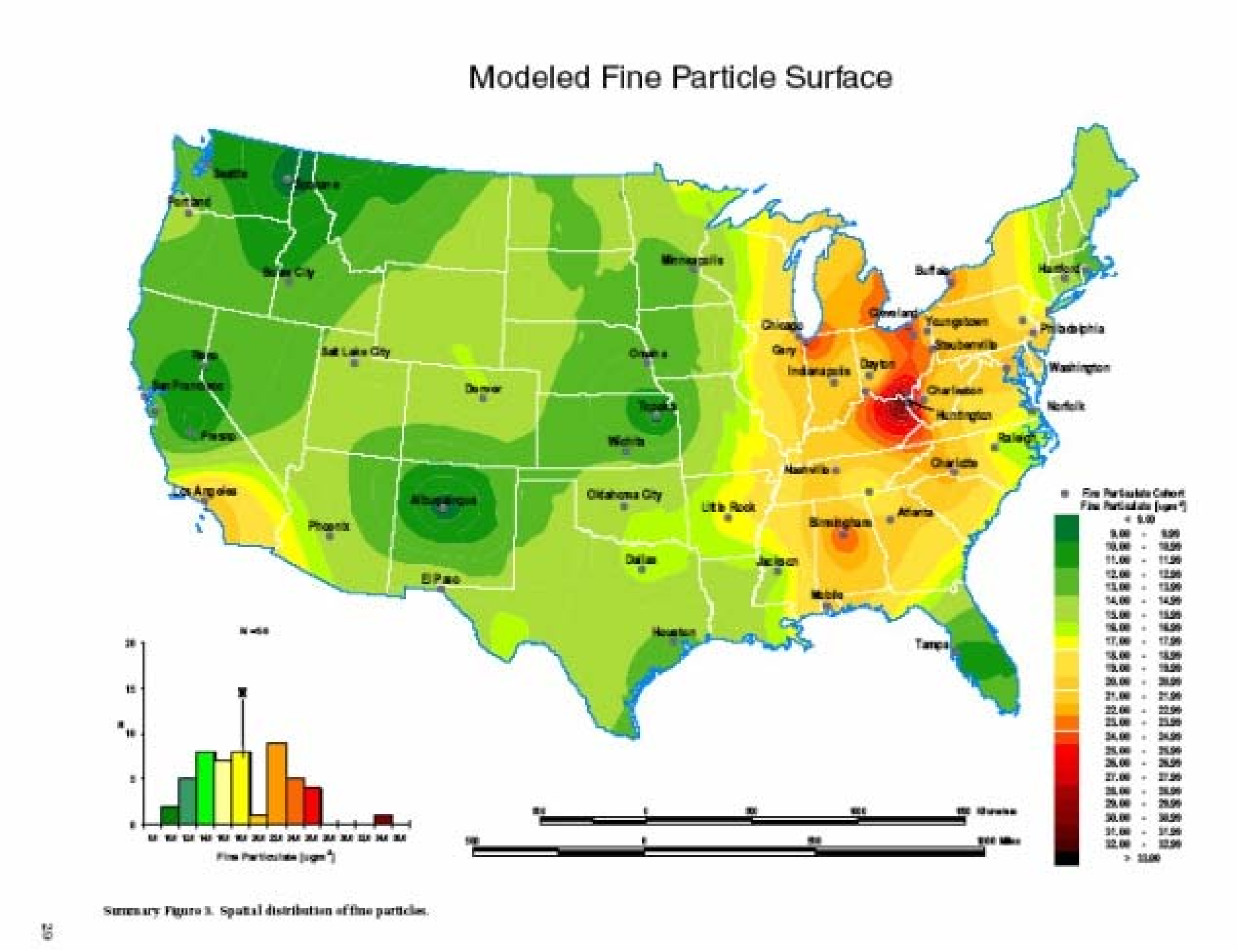

Figure 27. Geographical Distribution of $PM_{2.5}$ (8).

VITA

BEATRICE SIMO

Personal Data:	Date of Birth: April 29, 1976
	Place of Birth: Dschang, Cameroon
	Marital Status: Single
Education:	Bachelor in Foreign Applied Languages; University of Dschang, 1997
	Associate of Business Administration and International Management; University of Applied Sciences, Bremen, Germany 2002
	BBA General Management, East Tennessee State University; Johnson City, Tennessee, 2004
	MPH Epidemiology, East Tennessee State University; Johnson City, Tennessee, 2007
Professional Experience:	Graduate Assistant, East Tennessee State University; Johnson City, TN 2004-2006
	Research Assistant, East Tennessee State University; Johnson City, TN 2007